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ROLE OF AMPA RECEPTORS IN PHYSIOPATHOLOGICAL CONDITIONS IN THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

AMPA receptors play a key role in synaptic glutamatergic transmission in both physiological and pathological conditions of the central nervous system. Particularly, I have tried to analyze and to give some answers on aspects that are still unexplored or controversial using synaptosomes (pinched off nerve terminals) as experimental model.

As a first approach I focused on the composition of the GluA subunits, which is a requisite to encompass the role of AMPA receptors in the physiological conditions but also in neurological disorders. By using the "immuno- pharmacological approach", which consists in using antibodies recognizing the outer sequences of the target protein as a pharmacological tool, I propose that cortical AMPA autoreceptors consist of GluA2-GluA3 subunits assembly, which move in-out synaptosomal plasma membranes in a constitutive manner. The commercially available anti-GluA2 and anti-GluA3 antibodies hugely facilitated the releasing activity of the AMPA autoreceptors by stabilizing them in plasma membranes. Interestingly, the consequent presence of the antigen-antibody complex in synaptosomal plasma membranes caused the activation of complement through the classic pathway, then reinforcing the complement-induced evoked releasing activity of the immune complex in these terminals. The results unveiled therefore a *complement-dependent* and a *complement-independent* pathway that could account for central derangements and excitotoxic events occurring during central autoimmune diseases typified by anti-GluA autoantibodies overproduction. It is the case of patients suffering from the frontotemporal dementia (FTD) that have elevated levels of circulating anti-GluA3 autoantibodies. Contrary to expectation, however, the incubation of mice cortical synaptosomes with FTD patients' CSF (cerebrospinal fluid) positive for anti-

GluA3 autoantibodies causes the reduction of the glutamate release evoked by the agonist AMPA, instead of the predicted amplification. Further studies are required to address the point.

AMPA receptors are also potential targets of detrimental events in stress-related diseases, which are recapitulated by several animal models, including the perinatal restrain stress (PRS) rat model. By using this model, I investigated the long-term programming effects of PRS on the glutamatergic synapse in males and females. I demonstrated that male PRS rats displayed a reduced expression of GluA2 and GluA3 subunits in the dorsal hippocampus and prefrontal cortex in old age rats (20-22 months), in line with their impaired performance in the behavioral test. These results confirmed that the impaired glutamatergic transmission lie at the core of the pathological phenotype induced by PRS. Remarkably, the long-term programming effects triggered by PRS are strictly sex-dependent. Particularly, PRS mainly affects males whereas females seem to be protected against the detrimental effects triggered by early life stress.

Taken together these results strengthened the importance of understanding more about the role of AMPA receptors subunits in the brain functions.

RIASSUNTO

I recettori AMPA svolgono un ruolo chiave nella trasmissione glutamatergica sinaptica sia in condizioni fisiologiche che patologiche del sistema nervoso centrale. In questa tesi ho cercato di analizzare e dare alcune risposte su aspetti ancora inesplorati o controversi riguardanti questi recettori utilizzando come modello sperimentale i sinaptosomi (terminazioni nervose isolate).

Come primo approccio ho cercato di definire la composizione in subunità del recettore AMPA, un requisito necessario per comprendere il ruolo di questi recettori in condizioni fisiologiche ma anche nei disturbi neurologici. Usando anticorpi che riconoscono le sequenze esterne della subunità del recettore AMPA (GluA) come tool farmacologico ("approccio immuno-farmacologico"), ho dimostrato che gli autorecettori AMPA corticali sono costituiti dalle subunità GluA2 e GluA3 che trafficano in maniera costitutiva.

L'utilizzo degli anticorpi anti-GluA2 e anti-GluA3 ha determinato la stabilizzazione degli autorecettori AMPA a livello membranale con conseguente aumento dell'attività di rilascio indotta dall'agonista AMPA. Ho inoltre dimostrato che la conseguente formazione del complesso antigene-antcorpo (GluA/anti-GluA) nelle membrane sinaptosomiali attiva il complemento attraverso la via classica inducendo un aumento del rilascio di glutammato. I risultati hanno rivelato quindi un aumento di glutammato complemento-indipendente e complemento-dipendente che potrebbero spiegare le alterazioni a livello centrale e gli eventi eccitotossici osservati nel corso di malattie autoimmuni centrali caratterizzate dalla presenza di autoanticorpi anti-GluA. È il caso di pazienti affetti da demenza frontotemporale (FTD) che presentano un livello elevato di autoanticorpi circolanti anti-GluA3. Contrariamente alle aspettative, tuttavia, l'incubazione di sinaptosomi corticali di topi con CSF positivi per

autoanticorpi anti-GluA3 ha determinato una riduzione del rilascio di glutammato evocato dall'agonista AMPA, invece della prevista amplificazione. Saranno necessari ulteriori studi per meglio affrontare il problema.

I recettori AMPA sono anche potenziali bersagli degli eventi dannosi nelle malattie legate allo stress. Queste patologie possono essere studiate utilizzando diversi modelli animali, tra cui il modello di stress perinatale (PRS) su ratto. Utilizzando questo modello, ho potuto studiare gli effetti di programmazione a lungo termine del PRS sulla sinapsi glutamatergica sia nei maschi che nelle femmine. Ho dimostrato che i maschi PRS presentano un'espressione ridotta di GluA2 e GluA3 nell'ippocampo dorsale e nella corteccia prefrontale di ratti di età avanzata (20-22 mesi) in linea con le ridotte prestazioni osservate nel test comportamentale. Questi risultati confermano che l'alterata trasmissione glutamatergica è alla base del fenotipo patologico indotto dal PRS. Sorprendentemente, gli effetti di programmazione a lungo termine causati dal PRS sono strettamente dipendenti dal sesso. In particolare, i maschi risultano vulnerabili allo stress perinatale, mentre le femmine sembrano essere protette dagli effetti dannosi causati dallo stress precoce.

In generale, i risultati ottenuti durante il mio percorso di dottorato hanno rafforzato l'importanza di comprendere meglio il ruolo delle subunità dei recettori AMPA nelle funzioni cerebrali.

RESUME

Les récepteurs AMPA jouent un rôle clé dans la transmission glutamatergique synaptique aussi bien dans des conditions physiologiques que pathologiques du système nerveux central. Dans ma thèse, j'ai cherché à analyser et à apporter des réponses sur des aspects encore inexplorés ou controversés en utilisant des synaptosomes (isolation de terminaisons nerveuses) comme modèle expérimental. Dans une première approche, j'ai cherché à définir la composition des sous-unités GluA, qui est une condition nécessaire pour comprendre le rôle des récepteurs AMPA dans des conditions physiologiques mais aussi dans les troubles neurologiques. En utilisant des antcorps reconnaissant les séquences externes de la sous-unité du récepteur AMPA (GluA) comme outil pharmacologique («approche immunopharmacologique»), j'ai pu démontrer que les autorécepteurs corticaux AMPA sont constitués des sous-unités GluA2 et GluA3 qui se déplacent de façon constitutive.

L'utilisation des anticorps anti-GluA2 et anti-GluA3 a déterminé la stabilisation des autorécepteurs AMPA au niveau membranaire résultant en une augmentation de l'activité de libération induite par l'agoniste AMPA.

J'ai également démontré que la formation du complexe antigène-anticorps (GluA / anti-GluA) dans les membranes synaptosomales active le complément par la voie classique, induisant une augmentation de la libération de glutamate. Les résultats ont ainsi révélé des augmentations de glutamate indépendantes et dépendantes du complément qui pourraient expliquer les altérations centrales et les événements excitotoxiques observés dans les maladies auto-immunes centrales caractérisées par la présence d'autoanticorps anti-GluA. C'est le cas des patients atteints de démence frontotemporale (DFT) qui présentent un taux élevé d'autoanticorps anti-GluA3 circulants. Contrairement aux attentes, cependant, l'incubation de synaptosomes corticaux de souris avec un LCR positif pour les autoanticorps anti-GluA3 a entraîné une réduction de la

libération de glutamate évoquée par l'agoniste AMPA, au lieu de l'amplification attendue. Des études complémentaires seront nécessaires pour mieux résoudre le problème.

Les récepteurs AMPA sont également des cibles potentielles d'événements délètères dans les maladies liées au stress. Ces maladies peuvent être étudiées à l'aide de divers modèles animaux, y compris le modèle de stress périnatal (PRS) chez le rat. En utilisant ce modèle, j'ai pu étudier les effets de la programmation à long terme du PRS sur la synapse glutamatergique chez les mâles et femelles. J'ai montré que les mâles PRS présentent une expression réduite de GluA2 et GluA3 dans l'hippocampe dorsal et le cortex préfrontal de rats âgés (20-22 mois) en ligne avec la performance réduite observée dans le test comportemental. Ces résultats confirment que la transmission altérée du glutamate est à la base du phénotype pathologique induit par le PRS. De manière surprenante, les effets de programmation à long terme causés par le PRS dépendent strictement du sexe. En particulier, les mâles sont vulnérables au stress périnatal, tandis que les femmes semblent être protégées des effets néfastes du stress précoce.

De façon générale, les résultats obtenus au cours de mon programme de doctorat ont renforcé l'importance d'une meilleure compréhension du rôle des sous-unités des récepteurs AMPA dans le fonctionnement du cerveau.

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ABBREVIATIONS

[^{3}H]D-Asp [^{3}H]D-aspartate

ABP AMPA receptor-binding protein

ACTH Adrenocorticotropic hormone

ADAR2 adenosine deaminase acting on RNA

ALS Amyotrophic lateral sclerosis

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

APV arginine vasopressin

ATP adenosine triphosphate

CAMKII Ca^{2+}/calmodulin-dependent protein kinase II

CCR C-C Chemokine Receptor;

CNIH cornichon-like proteins

CNS central nervous system

CRH corticotropin-releasing hormone

CRP C-reactive protein

CSF cerebrospinal fluid

CUS chronic unpredictable stress

CNQX 6-cyano-7-nitroquinoxaline-2,3-dione

DL-t-BOA DL-threo-β-Benzyloxyaspartic acid

DMTs disease-modifying therapies

EAE experimental autoimmune encephalomyelitis

EPM elevated plus maze

ER endoplasmic reticulum

FTD frontotemporal dementia

GluA glutamate AMPA

GR glucocorticoid receptor

GRIP Glutamate receptor-interacting protein

HPA axis hypothalamic-pituitary-adrenal axis

IL-6/IL-1 interleukin-6/interleukin-1

INF γ interferon γ

IPSCs human induced pluripotent stem cells

KA kainite receptor

LBD ligand binding domain

LTD long-term depression

LTP long-term potentiation

MAGUK membrane-associated guanylate kinase

mGluR metabotropic glutamate receptor

MR mineralocorticoid receptor

MS multiple sclerosis

NBQX 2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide disodium salt

NMDA N-methyl-D-aspartate

NSF N-ethylmaleimide-sensitive fusion protein

PAM positive allosteric modulator

PND postnatal day

PICK1 protein interacting with C-kinase1

PKA cyclic AMP-dependent protein kinase

PKC protein kinase C

PRS perinatal restrain stress

PSD-95 postsynaptic density protein 95kDa

PVN paraventricular nucleus

RE Rasmussen's encephalitis

RRMS relapsing-remitting multiple sclerosis

SAP-97 Synapse-associated protein-97kDa

Stx-1A syntaxin-1A

SYP Synaptophysin

TARPs transmembrane AMPAR regulatory proteins

TM transmembrane

TNF- α tumor necrosis factor-alpha

VAMP vesicle-associated membrane proteins

VGLUT-1 vesicular glutamate transporter type 1

INTRODUCTION

1. AMPA receptors in the central nervous system

Synaptic plasticity is a central event for the normal functioning of the brain (Katz and Shatz, 1996). Brain development, learning and memory processes rely on changes in the excitatory synaptic strength (Bliss and Collingridge, 1993), which become stronger (long-term potentiation, LTP) or weaker (long-term depression, LTD) in response to different patterns of activity. The regulation of the synaptic strength at the excitatory synapse is typically expressed as a compensatory and bidirectional change in glutamate receptors. In the CNS, the receptors of glutamate can be divided into: receptors coupled to protein G, namely metabotropic glutamate receptors (mGluRs), and ligand-gated ion channels, namely ionotropic receptors. Thanks to the work of Watkins and Evans in 1981, the ionotropic glutamate receptors have been divided into three distinct subgroups based on their pharmacology: the quisqualate receptors, the N-methyl-D-aspartate (NMDA) receptors, and the kainate (KA) receptors. In 1980, Krogsgaard-Larsen and coworkers synthetized the compound α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), which was a more selective, potent, quisqualate-like agonist. This allowed further classification of the ionotropic glutamate receptor subtypes to give: AMPA receptors, NMDA receptors, and KA receptors (Collingridge and Lester, 1989; Lodge and Collingridge, 1990).

1.1 Structure of AMPA receptors

AMPA receptors are responsible for fast excitatory transmission and play a key role in synaptic plasticity. They are composed of four subunits, namely GluA1, GluA2, GluA3 and GluA4, encoded by different genes with 70% sequence homology. The subunits are assembled in tetrameric complexes with homomeric (four identical subunits) or heterodimeric (dimers of dimers) composition. GluA1, GluA2, and GluA3 subunits are enriched in the outer layer of the cerebral cortex, in the hippocampus, basal ganglia, olfactory regions, and amygdala (Keinanen et al., 1990; Beneyto and Meador-Woodruff, 2004). In hippocampal pyramidal cells, the vast majority of AMPA receptors are dimers of dimers of GluA1/GluA2 or GluA2/GluA3 with a smaller contribution from GluA1 homo-tetramers (Wenthold et al., 1996). As far as the GluA4 subunit is concerned, this is mainly expressed during development and mostly absent in mature excitatory neurons (Zhu et al., 2000). Interestingly, AMPARs were also found on glial cells (Janssens and Lesage, 2001).

Each subunit of the AMPA receptor comprises 900 amino acids and it is composed of four transmembrane (TM1 to TM4) domains, a large amino-terminal domain, and a small carboxyl-terminal domain. The TM2 forms a hairpin loop in the intracellular side of the plasma membrane so that the amino-terminal and the carboxy-terminal domain are intracellular and extracellular, respectively (Hollmann et al.,1994).

The amino-terminal domain and the loop between the TM3 and TM4 form the ligand binding domain (LBD), whereas the allosteric modulators act on a region in the TM3-4 loop (Greger et al., 2007). Upon the binding of glutamate, the LBD closes leading to the opening of the receptor gate. After activation, the receptor rapidly transits to the desensitized state (in 10ms; Armstrong et al., 2006), which means that the receptor becomes unresponsive to the agonist. Then the receptor switch to the closed state.

1.2 Post-translational modifications of AMPA receptors

The AMPA receptors are permeable to sodium and calcium ions whose influx causes fast excitatory postsynaptic responses in the neurons and whose conductance and kinetic properties depend on their composition in subunit. In particular, the permeability of calcium ions depends on the presence of the GluA2 subunit. Notably, the genomic DNA of this subunit encodes for glutamine (Q) at the level of the amino acid 607 in the TM2, but, when the mRNA of this subunit is subject to RNA editing, the glutamine 607 is replaced with the arginine (R; Sommer et al., 1991), and this change results in the modification of the kinetics and ions permeability of AMPARs. The receptors containing the edited GluA2 (R) subunit have a low permeability to calcium ions due to the positive charge of the arginine instead of the glutamine, whereas the receptors lacking GluA2 subunit or containing the unedited GluA2 subunit show a high permeability to ions and high conductance (Wright and Vissel, 2012). Actually, in the healthy adult brain, less than 1% of all RNA encodes unedited GluA2 (Q) subunits (Kawahara et al., 2003a). Abnormal low editing at this site has been implicated in different diseases of the central nervous system such as Alzheimer's disease (Gaisler-Salomon et al., 2014; Whitehead et al., 2017), epilepsy, ischemia and amyotrophic lateral sclerosis (Pellegrini-Giampietro et al., 1997; Kwak and Weiss, 2006). The downregulation of the edited GluA2 (R) subunits in these pathological conditions can result in cell death due to the increased permeability to calcium and the consequent activation of harmful calcium-dependent intracellular events.

The heterogeneity of the functional characteristics of AMPA receptors arises as well at the level of the loop between TM3 and TM4 to give the flip and flop splice variants. These variants differ for few amino acids but causes serious modification of the channel kinetics and desensitization proprieties. In particular, it's shown that the flip variant desensitizes four times slower than the flop one (Sommer et al., 1990; Mosbacher et al., 1994). Expression levels of the different splice variants are region and cell-type specific (Sommer et al., 1990). Besides the

extracellular splice variants, the subunits undergo alternative splicing also at the intracellular level to give long and short carboxyl-terminal domain isoforms. GluA2, GluA3 and the alternative splice form of GluA4 subunits have a shorter cytoplasmatic tail. In contrast, the predominant splice form of GluA1, GluA4, and the alternative splice form of GluA2 have a longer carboxyl-terminal domain. These isoforms are crucial for the surface expression and regulation of the trafficking of the receptors (deeply discussed in the next chapter; Song and Huganir, 2002; Malenka, 2003; Kessels and Malinow, 2009; Santos et al., 2009; Pick and Ziff, 2018).

1.3 Trafficking of AMPA receptors

1.3.1 Subunits assembly

AMPA receptors are dynamic entities continuously added and removed in and out of synaptic and/or extra-synaptic membranes in basal condition (with a half-life in the order of few minutes) as well as in response to neuronal activity (Song and Huganir, 2002; Esteban, 2003; Malenka, 2003; Henley et al., 2011; Henley and Wilkinson, 2016). Moreover, lateral movements allow the cycling of the AMPA receptors between the synaptic and extra-synaptic stores (Triller and Choquet, 2003). The change in the number of synaptic AMPARs plays a role in regulating the strength of synapses.

The trafficking of the receptor starts with its assembly in the endoplasmic reticulum (ER). The precise mechanism that governs subunits assembly is still unclear. However, evidence shows that the first step is the formation of dimers due to the interactions between the amino-terminal domain of the subunits (Nakagawa, 2010). The amino-terminal domain of GluA3 has a higher affinity for GuA2 subunit than for the self-assembly and the same is for

GluA1, thus favoring the formation of GluA3/GluA2 and GluA1/GluA2 associations, respectively. (Rossmann et al., 2011; Zhao et al., 2016). Actually, it has been shown that in GluA2 knockout mice hetero-tetramers or homo-tetramers of GluA1 and GluA3 subunits are preferentially expressed. However, these associations within subunits are less trafficked to the synapse compared to the physiological receptor composition (Sans et al., 2003).

The first step of the AMPA receptor assembly is followed by a second step that involves the ligand-binding and transmembrane domains, which intimately take part in the assembling of the tetrameric structure of the receptor.

Once the tetrameric structure is formed it exits from the ER. The specific site of exocytosis of AMPAR is still unclear (Shepherd and Huganir, 2007). Recent evidence suggests that the insertion of AMPAR in the synapse is provided by a large pool of extra-synaptic receptors that freely diffuse in the membrane (Granger et al., 2013; Penn et al., 2017). However, many studies also suggested that the insertion in the plasma membrane is dependent on the subunit composition of the receptor. The AMPA receptors containing long carboxyl tail (i.e. GluA1/GluA2 tetramers) exit the ER rapidly and require neuronal activity to be delivered to the synapse. In this case, when are present both GluA1 and GluA2, the receptor follows the trafficking rules of the GluA1 subunit. In general, long cytoplasmatic tail dictate the trafficking rules when present with a short C-tail (Shi et al., 2001). In contrast, GluA2/GluA3 heteromeric receptors (both bearing short cytoplasmatic tails) behave like GluA2 homo-tetramers and are retained longer in the ER due to the Q/R editing of GluA2 subunit (Greger et al., 2002). Once GluA2/GluA3 heterodimers exit the endoplasmic reticulum, they are inserted rapidly and continuously in basal conditions replacing GluA1-containing receptors after LTP (Passafaro et al., 2001; Shi et al., 2001).

Several auxiliary subunits, especially the transmembrane AMPAR regulatory proteins, (TARPs) and the cornichon-like proteins (CNH2/CNHI3), influence the maturation, the exit

from ER and the trafficking of the AMPA receptor complex (Tomita et al., 2003; Schwenk et al., 2009; Jackson and Nicoll, 2011; Brockie et al., 2013). TARPs are the most studied auxiliary subunits of AMPA receptors. In the rodent brain are present eight different TARPs, also called "γ" for the homology with the γ1 subunit of the voltage-dependent calcium channel. γ3, γ4, and γ8 are largely studied for their involvement in the AMPA receptor functions. Only a few years ago evidences were provided showing that also γ5 and γ7 are implicated in the regulation of the receptor (Kato et al., 2007, 2008; Soto et al., 2009). Among these proteins, the most studied is γ2, namely *stargazing.* The name derives from stargazer mice who display absence epilepsy and cerebellar ataxia due to the lack of AMPA receptors at the cerebellar granule neuron synapses (Chen et al., 1999; Hashimoto et al., 1999).

The first interaction between AMPA and TARPs is in the endoplasmic reticulum and this association masks an ER retention sequence of GluA subunits (Bedoukian et al., 2006) facilitating interaction within subunits but also stabilizing the assemblies intermediate. Interestingly, the interaction between TARPs and AMPARs stays stable from the exit from the ER to the insertion in the membrane. TARPs stabilize the receptor at the synaptic surface thanks to the interaction with PSD-95 (postsynaptic density protein 95kDa) and other MAGUK (membrane-associated guanylate kinase) scaffolds proteins (Nicoll et al., 2006). The phosphorylation of TARPS by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) facilitates the interaction of AMPAR with the PSD-95, then anchoring the receptor in the synapse (Sheng et al., 2018). Stargazin also influences AMPA receptor channel properties slowing the desensitization of the channel resulting in a potentiation of the glutamate evoked-currents (Priel et al., 2005; Tomita et al., 2005; Turetsky et al., 2005)

Similarly to TARPs, the cornichon proteins play a role in the receptor surface trafficking (Boudkkazi et al., 2014; Farrow et al., 2015) and operate as cargo for the export of the receptor from ER (Harmel et al., 2012; Brockie et al., 2013). These proteins intimately bind

the pore-forming GluA subunits in distinct regions of the rat brain such as the neocortex, the hippocampus and the cerebellum (Schwenk et al., 2009) and modify the channel kinetics of AMPA receptors by slowing deactivation and desensitization with a more significant effect than TARPs (Schwenk et al., 2009).

After exit ER, the AMPAR-containing vesicles traffic to the Golgi compartment where they undergo posttranslational modification such as glycosylation, palmitoylation, and phosphorylation (Jiang et al., 2006). In particular, the N-glycosylation of AMPA receptors protects them from proteolytic degradation and improves their maturation (Jiang et al., 2006), whereas if absent, it does not compromise the synthesis, assembly, or trafficking of the receptors. Moreover, recent evidence has shown a potential role of O-GlcNAcylation of the GluA2 subunit as modulator of hippocampal synaptic plasticity (Taylor et al., 2014). Phosphorylation of AMPARs, on the other side, is crucial for the activity of the receptor and the interaction with intracellular proteins, playing a role in the regulation of the mechanism involved in the synaptic plasticity (Soderling and Derkach, 2000). Palmitoylation is another relevant posttranslational modification of AMPA receptors. It regulates the stability of the receptors and protects them from degradation. AMPA receptors are palmitoylated at two sites, one within the pore (C858 in the TM-2 of GluA1), and the other one in the carboxyl-tail domain (C811 of GluA1). The palmitoylation in the TM-2 suppresses the delivery of AMPA receptors to the surface, accumulating the receptor in the Golgi apparatus (Hayashi et al., 2005). The de-palmytoilation activates receptor trafficking. Moreover, AMPA receptor palmitoylation is highly regulated by neuronal activity. The activation of the receptor mediated by glutamate diminishes the receptor palmitoylation increasing the insertion of the receptor in the membrane.

The secretory vesicles containing AMPA receptors, after being released from the Golgi, are trafficked to the plasma membranes, accordingly to the subunit-composition rules, presumably via kinesin- and dynein-dependent microtubule-associated (Hirokawa and

Takemura, 2005) and via myosin dependent motor transport (Osterweil et al., 2005). These subunit-specific rules have led to a model in which there are two different regulatory mechanisms that govern the insertion and removal of AMPA receptor from the synapse: the constitutive pathway, which involves GluA2/GluA3 subunits that are inserted directly into the synaptic surface, and the regulated pathway, which involves GluA1-containing receptors that are inserted into the synapse first entering the extra-synaptic membrane, and then diffusing laterally along dendrites to the synapse (Passafaro et al., 2001; Song and Huganir, 2002; Malenka, 2003; Kessels and Malinow, 2009; Santos et al., 2009; Pick and Ziff, 2018).

1.3.2 Trafficking from ER to plasma membrane

It is well established that the induction of LTP increases the number of AMPA receptors delivered to the synapse. On the contrary, LTD induces their internalization. Thus, it is clear that alterations in synaptic strength are directly related to the continuous cycling of the receptor at the synaptic surface.

LTP induction requires the calcium influx through the postsynaptic NMDA receptor that, in turn, activates CaMKII. The activated CaMKII phosphorylates the GluA1-containing receptors at the carboxyl-terminal domain. This cascade of events results in the augmentation of the synaptic incorporation and functioning of the receptor. In particular, CaMKII phosphorylates GluA1 subunits at Ser-831, which enhances the single-channel conductance of the receptor (Mammen et al., 1997). In addition to CaMKII, Ser-831 is also phosphorylated by PKC (Roche et al., 1996). However, mutations at Ser-831 that prevent the phosphorylation by CaMKII do not prevent the LTP-induced delivery of GluA1-containing receptor to the synapse (Hayashi et al., 2000). Moreover, other sites of the carboxyl-terminal domain of GluA1 are phosphorylated (Roche et al., 1996). In particular, the cyclic AMP-dependent protein kinase

(PKA) phosphorylates the Ser-845 in the carboxyl-terminal domain of GluA1 subunits resulting in an increased open-channel probability of the receptors (Banke et al., 2000), which correlates with changes in the synaptic strength (Lee et al., 2000). Furthermore, PKA controls the recycling in and out of the synapse of GluA1 (Esteban et al., 2003). Mutations at Ser-845 prevent the delivery of the GluA1 subunit to the synapse by active CaMKII (Lee et al., 2003). However, the activation of PKA alone cannot to induce the receptor exocytosis (Esteban et al., 2003).

Furthermore, the carboxyl-tail of GluA subunits have PDZ consensus motifs, which directly interact with PDZ-containing proteins. This interaction appears critical for the regulation of trafficking. In fact, mutations at the PDZ domain prevents the delivery of GluA1-containing receptor into synapses (Hayashi et al., 2000) and spines (Piccini and Malinow, 2002). However, the complete deletion of this domain is unable to affect the LTP (Kim et al., 2001). SAP-97 (Synapse-associated protein-97kDa) is the only protein known to interact with the PDZ motif of GluA1 subunits. This protein is a member of the MAGUK protein family, and it is related to PSD-95. CaMKII phosphorylates SAP-97, which in turn binds the PDZ-domain of GluA1 subunit in the ER until the arrival at the synapse (Sans et al., 2001) and stabilizes it in the synaptic membrane (Nakagawa et al., 2004). The interaction between the AMPA receptor and SAP-97 allows GluA1 to associate with other proteins such as PKA (Colledge et al., 2000) or NMDARs (Gardoni et al., 2003). Another protein, the 4.1N proteins, is a scaffolding unit that binds actin filaments stabilizing the GluA1-containing receptors at the synaptic surface by forming a complex with the carboxyl-terminal of the subunit.

While GluA1 is required for the activity-dependent delivery of AMPA receptors during LTP, GluA2/GluA3-containig receptors play a complementary role in the constitutive delivery pathway. The constitutive trafficking is relevant to maintain the synaptic strength in the absence of activity, being a molecular mechanism for memory consolidation. The trafficking

and the stabilization in membranes require cytosolic proteins, many of those have PDZ-domain. These proteins allow the continuous replacement of preexisting AMPARs with GluA2/GluA3-containing receptor at the synaptic level in an activity-independent manner. The GluA2 and GluA3 carboxyl-domain directly interacts with the PDZ-domain of GRIP (Glutamate receptor-interacting protein) and ABP (AMPA receptor-binding protein). These proteins anchor the receptors promoting their accumulation at the synaptic membranes (Dong et al., 1997) and impeding their internalization. Mice lacking a single residue in the PDZ-domain, which blocks the interaction with GRIP/ABP, show a diminished synaptic abundance of GluA2/GluA3 subunits. The same ligand site is shared with PICK1 (protein interacting with C-kinase 1) that regulates the receptor surface expression by driving the synaptic removal of GluA2-containing AMPARs during LTD (Kim et al., 2001; Perez et al., 2001; Hanley, 2008). Interestingly, the phosphorylation mediated by PKC on Ser-880 or Tyr-876 disrupts the complex GluA2 (or GluA3)-GRIP/ABP but not GluA2-PICK1 (Chung et al., 2000). Besides the previously mentioned proteins, GluA2 carboxyl-terminal domain also interacts with N-ehtilmaleimide-sensitive fusion protein (NSF, Osten et al., 1998; Song et al., 1998) resulting in a rapid stabilization at the synaptic site. NSF disassembles PICK1 from GluA2 C-tail, facilitating the delivery and the maintenance of the receptor at the synapse.

While increased synaptic delivery of AMPA receptors underlines LTP, LTD involves the removal or loss of synaptic AMPA receptors. The first evidence was provided by Carroll and coworkers in 1999 who showed that the NMDAR-dependent LTD in the hippocampal cell culture was associated with a reduction in the synapse of the number of GluA1-containing receptors (Carroll et al., 1999). Not only the receptor internalization, but also the phosphorylation of AMPA receptors is relevant to LTD. Ser-845, but not Ser-831, during LTD is dephosphorylated (Lee et al., 2000), and this regulates the AMPA receptor internalization. Interestingly, mice lacking phosphorylation at both Ser-831 and Ser-845 show a deficit in LTD

and in AMPAR endocytosis (Lee et al., 2003), suggesting an essential role for the phosphorylation processes in dictating the synaptic plasticity.

In addition to GluA1, Glua2/GluA3 subunits are especially involved in LTD. In fact, the number of these receptors diminishes during LTD due to their binding to the adaptor protein AP-2 that shares the same site of interaction of NSF. The blockade of NSF leads to a significative reduction of AMPAR excitatory postsynaptic currents, which is followed by a significant reduction in the expression of GluA2-containing AMPARs at the cell surface (Nishimune et al., 1998; Noel et al., 1999). Furthermore, PICK1 and the phosphorylation mediated by PKC trigger the internalization of GluA2/GluA3-containing receptors giving their contribution to the induction of LTD.

1.4 Presynaptic release-regulating AMPA receptors

The first evidence in the literature suggesting the existence of presynaptic release-regulating AMPA receptors dates 1991 when Cheramy and colleagues demonstrated that the exposure of synaptosomes isolated from the striatum to (RS)AMPA elicits a Ca^{2+}-dependent release of preloaded [^{3}H]dopamine that was detectable in the presence of Mg^{2+} ions (then excluding the possible involvement of NMDA receptors as well) and prevented by broad spectrum glutamate antagonist (Cheramy et al., 1991). Starting from this first observation, evidences were provided by different laboratories during years supporting this conclusion. These studies unveiled the presence of presynaptic AMPA autoreceptors in the cortex and hippocampus and of AMPA heteroreceptors in cholinergic, GABAergic, noradrenergic and serotonergic terminals (Desce et al., 1991; Sherman et al., 1992; Barnes et al., 1994; Pittaluga et al., 1994, 1997; Perkinton and Sihra, 1999; Ghersi et al., 2003). These functional observations were paralleled by findings unveiling the active delivery of AMPA receptors in

plasma membranes (Schenk et al., 2003) that was demonstrated to rely on a constitutive trafficking of GluA2-subunit containing receptors (Pittaluga et al., 2006; Summa et al., 2011; Grilli et al., 2012; Cisani et al., 2021). Almost concomitantly all the components of the synaptic machinery (e.g. GRIP1, PICK1, NSF) required to assure the constitutive in-out movements of AMPA receptors was proven to be expressed in synaptosomes and to be associated to the GluA 2 subunits (Haglerød et al., 2009, 2017).

Observations were then collected demonstrating that presynaptic AMPA receptors containing GluA2 subunits, which traffic constitutively in-out synaptic membranes are widely expressed in nerve endings. Inasmuch, a direct correlation was proven to exist between the trafficking of AMPA receptors and their releasing activity, supporting the notion that the efficiency of the AMPA-evoked transmitter overflow strictly depends on the number of receptors inserted in the synaptic membranes. This correlation was found for AMPA receptors controlling the release of different transmitters (noradrenaline; dopamine; glutamate) in several regions of the CNS including cortex, hippocampus and nucleus accumbens (Pittaluga et al., 2005; Summa et al., 2011; Grilli et al., 2012; Cisani et al., 2021). So far unanswered question still concerns the prediction of the subunit composition of the AMPA receptors. The available ligands are not sufficiently selective towards the different subunits and do not allow to predict the participation of a specific protein to the expression of the receptor. Nonetheless, the results obtained with these ligands suggest that presynaptic release regulating AMPA receptors can be roughly subdivided in two major categories as follow:

i) AMPA receptors that are prone to desensitization (either cyclothiazide or concanavalin-A sensitive processes), that traffic in-out the synaptic membranes and usually involves the GluA2 subunits in the receptor assembly. These AMPA receptors control glutamate, dopamine, and noradrenaline release and are sensitive to the acidification of the external milieu (Pittaluga et al., 1997, 2005; Ghersi et al., 2003).

ii) AMPA receptors that do not desensitize when exposed subsequently to the agonist, that are insensitive to the concomitant addition of anti-desensitizing agents (i.e. cyclothiazide or concanavalin-A sensitive processes), that do not traffic in a PICK1-dependent constitutive manner and that are largely insensitive to the acidification of the external milieu. These AMPA receptors control the release of GABA and acetylcholine belong to this class. These observations led us to propose that the receptors consist of subunits assembly that should not involve the GluA2 subunits.

2. AMPA receptors in neurodegenerative disorders

Glutamatergic neurotransmission is essential for brain function. Malfunction of the excitatory synapse, disrupted neuronal circuits, altered synapse structures and abnormal glutamate receptors functions or expression are implicated in many neurological and neurodegenerative diseases (Chang et al., 2012; Henley and Wilkinson, 2016). The excessive or prolonged stimulation of the excitatory receptors due to an immoderate release of glutamate causes nerve cell damage or death (Olney, 1969). The toxic effects of glutamate were first observed by Lucas and Newhouse (1957) who described the degeneration of the inner layers of the retina following subcutaneous injections of glutamate in infant mice. Over the years, studies have demonstrated the involvement of glutamate in the mechanisms of neuronal death in different acute neurodegenerative conditions, such as stroke and traumatic brain injury (Kwak and Weiss, 2006; Szydlowska and Tymianski, 2010; Weiss, 2011; Wright and Vissel, 2012). Moreover, glutamate was also proposed as a key mediator in the pathogenesis of a number of chronic neurodegenerative diseases, including motor neuron disease such as amyotrophic lateral sclerosis (Plaitakis, 1990; Leigh and Meldrum, 1996) and multiple sclerosis (Bolton and Paul, 1997; Pitt et al., 2000; Smith et al., 2000; Groom et al., 2003).

Glutamate receptors, including the AMPA ones, may therefore be crucial factors in several central diseases considering their main role in mediating most of the excitatory transmission in the CNS.

2.1 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease generally occurring after the age of 50 years, even if also younger patients can be affected. The hallmark of the pathology is the progressive degeneration of the upper motor neurons in the cortex and the lower motor neurons in the spinal cord. The initial symptoms are muscle wasting and weakness, generalized fasciculations, swallowing difficulties and dyspnea. It is a progressive disease, which leads to paralysis. Typically, death is due to respiratory failure and it is estimated to occur between 3-5 years from the symptom onset.

The incidence of ALS in Europe is 2-3 people per 100,000 individuals (van den Berg, 2014), and the lifetime risk of developing ALS in the United States and Europe is about 1:400 (Johnston et al., 2006). The 10% of Amyotrophic lateral sclerosis cases are classified as "familial" ALS (fALS) since there is a mendelian pattern of inheritance, whereas the remaining (around 90%) are known as "sporadic" ALS (sALS).

The etiology of the non-hereditary form of amyotrophic lateral sclerosis is still unknown. It is widely accepted that the ALS is a multifactorial pathology with different mechanisms of motor neuron death. One of these is the hyperactivation of the glutamatergic system at the level of the spinal motor neurons that causes excitotoxicity (Leigh and Meldrum, 1996; Bogaert et al., 2012; Bonifacino et al., 2019). The molecular mechanism has been proposed to rely on cytosolic calcium overload in combination with a reduced intracellular calcium buffering capacity. The increased calcium influx causes the activation of a number of Ca^{2+}-dependent enzymes, the collapse of membrane potential, and the alteration of the osmotic gradient of the cell leading to water influx. These events result in a massive proteolysis, mitochondrial disruption, and cells swelling. Ultimately, the cell membrane ruptures, and the intracellular contents are released, causing the death of the motor neuron (Patai et al., 2017).

In the ALS, the high influx of calcium ions can occur through the AMPA receptor channels and it depends on the presence of the GluA2 subunit. In the healthy adult brain, when this subunit is involved in the receptor assembly, the AMPA receptor is mainly calcium impermeable as a result of GluA2 mRNA editing at the Q/R site (Sommer et al., 1991). When the GluA2 subunit is not present, the receptor become permeable to calcium. Only a small percentage of the GluA2 subunit does not undergo the mRNA editing, resulting in high intracellular calcium entry (Kawahara et al., 2003a).

Thus, the high level of intracellular calcium in ALS can be due to two different mechanisms involving the AMPA receptors and in particular the GluA2 subunit. The first one is a reduced expression of the GluA2-containing receptors resulting in an increased number of AMPA receptors permeable to calcium. The second is a reduction of GluA2 editing efficiency, which implies that the receptor inserted in the plasma membrane contains the unedited GluA2 subunit (Kwak and Kawahara, 2005). Quantitative analysis of AMPA receptor mRNA revealed that motor neurons of sporadic ALS patients express the same amount of GluA2 mRNA respect to control (Kawahara et al., 2003b). Since there is not a reduced expression of GluA2 subunits, this could not be the mechanism underlying AMPA-receptor mediated motor neurons death in amyotrophic lateral sclerosis.

Conversely, the second hypothesis is the likely one. In fact, several studies demonstrated that in the motor neurons of sporadic ALS, the RNA editing of the GluA2 subunit is inefficient (Takuma et al., 1999; Kawahara et al., 2004; Kwak and Kawahara, 2005). Accordingly, recent works have shown that in the sporadic ALS there is a downregulation of the editing enzyme adenosine deaminase acting on RNA (ADAR2; Hideyama and Kwak, 2011; Hideyama et al., 2012), which is the principal responsible for the RNA editing at the Q/R site of the GluA2 subunit. The dysfunction of the ADAR2 leaves the GluA2 subunit unedited, thereby making the receptor permeable to calcium.

Notably, in spinal motor neurons, the expression of the GluA2 subunits is relatively lower than in other neuronal subsets (Kawahara et al., 2003b). Thus, the reduced RNA editing in ALS spinal motor neurons leads to an increase in the proportion of unedited GluA2-containing receptors making the spinal motor neurons more vulnerable.

2.2 Stroke

Stroke is a leading cause of long-term disability. It occurs when a blood vessel is occluded, resulting in an immediate loss of oxygen, glucose, and all other nutrients needed to support brain metabolism.

Although stroke is generally classified as deprivation of oxygen and glucose through inadequate blood delivery to the brain, it can occur in various forms. A small percentage (around 15%) of stroke can be “hemorrhagic”. This form depends on the rupture of a blood vessel, which leads to the bleeding into the brain tissue. Differently, the most common form of stroke, which represents the remaining 80-85%, is the ischemic stroke. This form generally occurs when the blood flow to an area of the brain is reduced or even ceased as a result of a vessel occlusion by a thrombus or embolus (Falluji et al., 2012).

Ischemic stroke is characterized by a complex cascade of events that rapidly initiate and that can last even days (Moustafa and Baron, 2008).The severity of each case depends on different factors, including the presence and effectiveness of collateral circulation, the area of the brain damaged and its severity, and numerous other factors. In general, stroke led to the dysfunction and death of brain neurons, causing irreversible neurological damage in the ischemic core. The ischemic core, or necrotic core, is the area of the brain immediately surrounding the tissue where the blood flow is interrupted (Schaller and Graf, 2004). The tissue in the ischemic core is irreversibly injured, and it does not have the potential to recover. In fact,

in this area, the blockage of the circulation causes the rapid death of the neurons. The necrotic core is surrounded by tissue, that, even if damaged and hypo-perfused, is still metabolically active; this is known as the ischemic penumbra area (Schaller and Graf, 2004). The cells within the penumbra have enough energy to survive for a short period but not enough to maintain their function for longer (Hakim, 1998). Therefore, since the tissue within the penumbra is not necessarily fated to die, this is the region in which there is the possibility to recover the cell's functions via post-stroke therapy (Ginsberg, 2003; Markus et al., 2004).

During the years, different studies regarding the central mechanism underlying neuron death in stroke have highlighted the importance of the excitotoxicity (Rothman and Olney, 1986; Choi and Rothman, 1990; Siesjo et al., 1995; Soundarapandian et al., 2005; Hu and Song, 2017). After the onset of a stroke, the blockage, or the reduction of the blood flow in the brain causes oxygen and glucose deprivation. This event drastically reduces the cellular production of ATP (Katsura et al., 1994; Martin et al., 1994), which in turn causes an accumulation of protons and lactate (Martin et al., 1994), resulting in rapid cellular acidification and enhanced depletion of ATP. If the level of the adenosine triphosphate is low, the Na^+/K^+-ATPase function fails. This failure, in turn, causes the activation of the voltage-gated calcium channels, which leads to an excessive release of excitatory neurotransmitters (i.e. glutamate) in the extracellular side (Rothman and Olney, 1986). Simultaneously, the neurotransmitter re-uptake capability is reduced (Rossi et al., 2000; Camacho and Massieu, 2006). The consequence is an excessive release of glutamate at the level of the synapse, which over-activates the ionotropic glutamate receptors causing a massive entry of calcium ions, which lead to neuron death.

Several observations suggest that AMPA receptors could play a key role in the neurodegeneration that occurs after the ischemic insult. In hippocampal pyramidal neurons, and in particular in the CA1 region, following ischemia, there is an increased number of calcium-permeable AMPA receptors (Anzai et al., 2003). The increased surface expression of

AMPA receptors permeable to calcium correlates with the increased vulnerability to neuronal death.

Also, the complexes GluA2- GRIP/ABP and GluA2-PICK1 are implicated in this mechanism. Ischemia disrupts the interaction of the GluA2 subunit with GRIP/ABP, favoring the PCK1 binding within the subunit (Liu et al., 2006), causing, therefore, the endocytosis of the GluA2 subunit and thus, a decreased surface expression of calcium-impermeable AMPA receptors (Dixon et al., 2009). In addition to surface loss, studies have demonstrated that in the CA1 region, there is a selective downregulation of GluA2 mRNA after an ischemic insult (Pellegrini-Giampietro et al., 1997). This downregulation leads to a reduced expression of AMPA receptors containing the GluA2 subunit, and consequently, to an increased expression of AMPA receptors permeable to calcium (i.e. GluA3/GluA1; GluA1/GluA4). Specifically, the decrease of the GluA2 subunit expression is due to the increased neuronal transcription factor REST (repressor element-1 silencing transcription factor; Calderone et al., 2003), which suppresses GluA2 gene expression.

Moreover, recent evidence has suggested that GluA2 RNA editing deficiency also occurs in ischemia (Peng et al., 2006). This event favors the incorporation of unedited GluA2 subunit in the composition of the receptors, making them permeable to calcium. Interestingly, the CA1 region seems to be the most vulnerable region to the ischemic insult since neither ADAR2 deficiency nor death cells was observed in the CA3 region (Peng et al., 2006).

Therefore, the blockage of the calcium permeable AMPA receptor is proposed as a suitable mechanism to protect neurons following ischemia. It has been shown that the AMPA receptor antagonist NBQX (2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide disodium salt), when given by intraperitoneal injections, significantly increases the cell survival within the CA1 region (Buchan et al., 1991). More recently, Noh and colleagues in 2005 demonstrated that the administration of Naspm (1-Naphthylacetyl spermine

trihydrochloride), which blocks the AMPA receptors permeable to calcium, ameliorate the viability of the cells in the same region (Noh et al., 2005). Furthermore, the exogenous delivery of the ADAR2 gene or the expression of active CREB (cAMP response element-binding protein), which induces ADAR2 expression, was also shown to restore the GluA2 editing and to save neurons from the cellular death due to the ischemic insult (Peng et al., 2006).

3. AMPA receptors in neuroimmune disorders

Neuro-immunological research conducted during the last years has provided new insights in the role of brain inflammation in neurological and neuropsychiatric diseases. Dysfunction of the immune system can cause autoimmune diseases, chronic inflammation, and cancer. The immune system is a complex integrated network of chemical mediators and cells, biological structures, and processes, developed during evolution to defend the organism from any form of chemical, traumatic or infectious insult (McComb et al., 2019).

Humans and other species have two major subsystems of the immune system: the innate and adaptive immune systems . The first is the ancestral immunity, which has been developed and perfected during evolution and represents the older and the first line of defense of our body. It is also capable of recognizing a very limited number of receptors, using sensors encoded by genes already present in germ cells and expressed in all cell types(Ransohoff and Brown, 2012; Waisman et al., 2015).

Adaptive immunity relates to the immune-mediated signals mediated by immune-competent cells (B and T lymphocytes) whose production and circulation is increased after the exposure of the subject to a pathogen or in general to a component antigenic in nature, which causes an immunological memory that assure a long-last cell-mediated protection towards the triggering signals (Waisman et al., 2015).

3.1 AMPA receptors and autoimmune neurological disorders

Over the past 20 years, several CNS disorders affecting the hippocampal and the cortical functions have been shown to associate to the production of autoantibodies recognizing synaptic proteins, ion channels, or neuronal receptors such as NMDA receptors, AMPA receptors, GABAA receptors, and dopamine D2 receptors. The evidence originated from the identification of antigen-specific CNS immune responses in a rare group of cancer-triggered disorders, named paraneoplastic syndrome (Corsellis et al., 1968; Zaborowski and Michalak, 2013; Höftberger and Lassmann, 2018). In these classical paraneoplastic encephalitides, the target antigens are intracellular, and the immunocompetent events appear to be mediated by cytotoxic T-cell mechanisms. More recently, however, evidence suggested that the antibodies to the cell surface or synaptic proteins prevail over the antibodies direct against intracellular antigens described in paraneoplastic disorders (Graus et al., 2008).

The presence of autoantibodies correlates to memory deficits, emotional and behavioral abnormalities such as confusion, irritability, depression, sleep disturbances, psychiatric symptoms as well as seizures and sometimes dementia. Some of the patients also develop a generalized encephalopathy with movement disorders and decreased consciousness. The causative link between the production of the autoantibodies and the neurological symptoms still represents a matter of discussion (Rhoads et al., 2011; Titulaer et al., 2013; Khandaker et al., 2015).

Several mechanisms may account for the pathogenicity of autoantibodies. It is proposed that autoantibodies can cause changes in the insertion, localization, and function of the respective antigens or that they can trigger complement-mediated neuronal damage. One or more of these effects contribute to the disease process in different autoimmune disease of the CNS.

3.1.1 Rasmussen's encephalitis and anti-GluA antibodies

Rasmussen's encephalitis (RE) was first described by Theodore Rasmussen and colleagues in 1958. It is a severe and chronic brain disorder mainly affecting children or young adolescents, with a mean age of 6 years. The histopathological hallmarks are neuronal cell loss, gliosis, and T cell infiltrates confined to one cerebral hemisphere (Varadkar et al., 2014). The Magnetic resonance imaging of children affected by RE highlights the diffusion of cortical inflammation throughout one of the two hemispheres. The onset of the pathology is characterized by frequent focal seizures refractory to antiepileptic drugs, which can often progress to "epilepsia partialis continua" (Thomas et al., 1977; Longaretti et al., 2012). When the pathology is untreated, children develop hemiparesis, hemianopia, and neurological and cognitive decline. If the left hemisphere is affected, they also display dysphasia. The end-stage of the pathology is characterized by severe neurological deficit, motor and cognitive impairment and death.

To date, the only cure remains surgery and the complete disconnection of the affected hemisphere (hemi-disconnection; Kossoff et al., 2003; Tubbs et al., 2005; Marras et al., 2010). The surgery leaves the child free of seizures but with severe neurological deficits.

In few cases plasmapheresis blocks the status epilepticus and neurological deterioration (Rogers et al., 1994; Andrews et al., 1996), supporting the hypothesis of an immune-mediated pathogenesis of Rasmussen's encephalitis, as first hypothesized in 1994 by Rogers and coworkers (Rogers et al., 1994). In their pioneristic work, these authors immunized four rabbits with the GluA3 fusion proteins and two of them developed a high titer of anti-GluA3 autoantibodies. Concomitantly, the animals displayed recurrent seizures and cortical inflammation characterized by microglial nodules and lymphocytic infiltrates (Rogers et al., 1994). Based on the fact that these signs are also hallmarks of Rasmussen's encephalitis, it was

proposed that the presence of anti-GluA3 autoantibodies could be intimately linked to the onset of the disease. To test the hypothesis, the authors measured the presence of the anti-GluA3 antibodies in the sera of patients suffering from RE. They found that the sera of three out of four patients reacted with cells transfected with plasmids containing the complementary DNA for GluA3. The sera of control patients didn't react with the transfected cells (Rogers et al., 1994) to indicate a correlation between Rasmussen's encephalitis and anti-GluA3 antibodies. In line with this hypothesis, they also found that the quality of life of patients improved transiently after plasma exchange, which removes the circulating antibodies. Later, in 1996 Andrews and colleagues confirmed the efficacy of the plasmapheresis in RE patients (Andrews et al., 1996), sustaining the assumption that Rasmussen's encephalitis is an immunopathological-mediated disorder and that anti-GluA3 antibodies play a pathogenic role in the disease by causing cytotoxicity in the brain.

Two are the authors that deeply discussed the mechanism of cytotoxicity induced by anti-GluA3 autoantibodies. In 1995, Twyman and coworkers showed that the presence of antibodies direct against the GluA3 subunit of AMPA receptors evokes excitatory currents in cultured mouse cortical neurons that are blocked by CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), an AMPA receptor antagonist. Thus, they hypothesized that the anti-GluA3 antibodies act as full agonists of the AMPA receptors resulting in hyperexcitability and seizure activity (Twyman et al., 1995).

Few years later Whitney and McNamara found that the anti-GluA3 antibodies are also able to cause a complement-mediated neuronal death. The activation of the complement was proposed to rely on the formation of the membrane attack complex, which forms transmembrane channels. The formation of these channels was proposed to be essential to the disruption of the cell membrane, cell lysis, and, in the end, to the death of the target cells (Peitsch and Tschopp, 1991; Alexander et al., 2008). Moreover, the presence of the channels

allows the influx of calcium, which in turn promotes the hyperexcitability and seizures that are the hallmark of Rasmussen's encephalitis.

Indeed, even if it is now considered that T-cell-mediated damage of astrocytes and neurons is the most likely primary event in Rasmussen's encephalitis (Bien et al., 2002a, 2002b; Schwab et al., 2009), perhaps the antibodies-mediated events remain relevant to the inflammatory state occurring during the disease.

It is worth stressing that anti-GluA3 antibodies were subsequently detected not only in the sera of RE patients but also in biological fluids from patients suffering from other central pathologies (as illustrated below), suggesting that they do not represent a hallmark of the RE.

3.1.2 Frontotemporal dementia and anti-GluA antibodies

Frontotemporal dementia (FTD) is the third common form of dementia across all age groups (Bang et al., 2015). Based on the dominant clinical presentation FTD is classified into two main clinical variants: behavioral-variant frontotemporal dementia (bvFTD) typified by personality changes and socially inappropriate behavior, and primary progressive aphasia (PPA), where the patient presents a dramatic deterioration in language skills. PPA is further divided based on the pattern of language failure into non-fluent variant, semantic-variant, and logopenic aphasia (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Since the course of the pathology is progressive, the clinical symptoms of the different variants can converge, resulting in cognitive impairment and motor deficits such as difficulty in eating and swallowing. Usually, death is due to secondary infection and is estimated to occur within 8 years from the symptom onset.

Frontotemporal dementia is characterized by the atrophy of the frontal and temporal lobes, subcortical gliosis, and neuronal loss. The neuropathological hallmarks of the FTD are

the abnormal proteins deposition and, in particular, the deposition of tau, TAR DNA-binding protein 43 (TDP-43), or fused-in-sarcoma (FUS) protein (Spillantini and Goedert, 2013; Neumann and Mackenzie, 2019). The corresponding pathological subtypes are frontotemporal lobar degeneration-Tau (FTLD-Tau), FTDL-TPD, and FTLD-FUS. The first and the second pathological subtypes account for over 90% of the cases. Several studies based on knockout approach have been conducted to elucidate the etiology of the disease. In this context, it has been observed that mutations of *Microtubule Associated Protein Tau (MAPT)* cause tau accumulation and that *Granulin (GRN)* or expansion *chromosome 9 open reading frame 72 (C9orf72)* are associated with TPD-43 proteins deposition (Borroni and Padovani, 2013). These mutations account for 60% of all cases of inherited frontotemporal lobar degeneration (Le Ber, 2013). However, it is still unclear if tau, TDP-43, and FUS proteins deposition represent the trigger mechanism or the consequence of other events.

In recent years, the hypothesis that neurotransmitters have a role in the pathogenesis of the disease came to interest of the researcher. Actually, FTD is characterized by dysregulation of serotonin, dopamine, GABA, and above all, glutamate systems (Murley and Rowe, 2018). Hoover and coworkers found that the accumulation of tau in dendritic spines of transgenic mice expressing human tau containing the P301L mutation affects the synaptic localization of glutamate receptors, and in particular of NMDA and AMPA receptors (Hoover et al., 2010). The same results is also observed using transgenic mice expressing a different tau mutation (Warmus et al., 2014). The behavioral abnormalities of these mice is reverted following NMDA agonist treatment (Warmus et al., 2014). This result supports the role of impaired glutamate receptor localization as a mechanism of tauopathy. Also, in transgenic mice expressing mutations in the FTD-associated gene *CHMP2B (charged multivesicular body protein 2b),* the AMPA receptors composition is altered. The mutation downregulates the miR-124 resulting in increased GluA2 subunit expression levels (Gascon et al., 2014). This event

causes an imbalance between Ca^{2+}-permeable and Ca^{2+}-impermeable AMPARs, which is linked to the altered social behavior typical of the FTD (Gascon et al., 2014). The ectopic miR-124 expression in the cortex of transgenic mice decreases the AMPA receptors levels and partially reverts the behavioral deficits. The same effect is obtained by knocking down animals for *Gria2* gene (Gascon et al., 2014). However, not only GluA2 subunit seems to be involved in the pathogenesis of FTD. Evidences suggested that *FUS* depletion, which causes FTLD-like behavior, downregulates the transcription of the GluA1 subunit of the AMPA receptor, thus affecting the synaptic transmission and the LTP (Udagawa et al., 2015).

In addition to preclinical evidence, the post-mortem analysis of the frontal and temporal lobes of FTD patients shows reduced AMPA and NMDA receptor density (Procter et al., 1999; Bowen et al., 2008) and altered AMPA receptor composition at the synaptic level (Gascon et al., 2014). Also, the magnetic resonance spectroscopy of patients suffering from FTD reveals that the glutamate/glutamine ratio is reduced in the frontal and temporal lobes (Ernst et al., 1997), supporting the role played by the neurotransmitters in the pathogenesis of the disease.

Interestingly, a new player in the FTD pathogenesis came to the interest of the researchers. Evidence suggests a link between FTD and autoimmunity (Sjögren and Wallin, 2001; Weintraub et al., 2006; Miller et al., 2013; Burberry et al., 2016; Cavazzana et al., 2018). Recently, Borroni and colleagues, identify the presence of anti-GluA3 autoantibodies in a significant number of FTD cases, both in serum and CSF. The treatment of hippocampal rat neurons and differentiated neurons from hiPSCs (human induced pluripotent stem cells) with the CSF of patients positive for anti-GluA3 antibodies titer induces a reduction of the density of the GluA3-containing receptors at the post-synaptic level, with no alteration of the GluA3 subunit clusters density (Borroni et al., 2017). The presence of antibodies raised against the GluA3 subunit also is able to cause the reduction of the dendritic spine density (Borroni et al., 2017). Since AMPA receptors are involved in the synaptic plasticity by maintaining the

dendritic spines at the glutamatergic synapse (Chater and Goda, 2014), the observed reduction of dendritic spine density suggests that autoantibodies cause not only molecular event at the receptor level but also a profound alteration of neuronal function, which correlate with the cognitive impairment. Thus, the identification of anti-GluA3 autoantibodies both in serum and CSF of FTD patients support the autoimmune hypothesis as a possible cause of FTD. We will detail the role played by anti-GluA3 antibodies in FTD patients in chapter 2 of results.

3.1.3 Multiple Sclerosis and anti-GluA antibodies

Multiple Sclerosis (MS) is a disorder of the central nervous system with unknown etiology. It is typified by autoimmune attack direct against antigens associated with myelin, neuro-inflammation, and synaptic derangements. The course of multiple sclerosis is highly variable. In most patients, the early stages of the disease are characterized by recurrent neurological symptoms followed by total or partial recovery. This is the "relapsing-remitting multiple sclerosis" form of the disease (RRMS). After 10–15 years of disease, the patients develop a progressive neurological decline that occurs independently from relapses. This disease stage is defined as secondary progressive multiple sclerosis (SPMS). However, in a small percentage of individuals suffering from MS, the disease progression is relentless from the onset (i.e. the primary progressive MS, PPMS; Lublin et al., 2014).

It is proposed that multiple sclerosis is initiated and sustained by the peripheral immune responses targeting the CNS, which drive the disease during early phases. Concomitantly, the modulation of the autoimmune attack, probably mediated by the infiltrating T regulatory cells themselves, participates in the onset and maintenance of the pathology. In particular, the proinflammatory and regulatory leucocytes are recruited into the inflamed tissues where they released chemokines (Karpus and Ransohoff, 1998; Ransohoff et al., 2007). Accordingly, the

augmented expression of selected chemokines such as CCL5 or CXCL12, represent a predictive marker of the progression of the disease (Godiska et al., 1995; Sørensen et al., 1999; Besong et al., 2002; Pittaluga, 2017).

Inflammation and demyelination are thought to be of major importance in the progression of the disease. However, the neurological features of this pathology, such as loss of synaptic contact, axonal pruning, and astrocytosis suggest a critical contribution of axonal and neuronal impairment in the progression of the disease. It has been recently accepted that the inflammation and neurodegeneration are intertwined and not one the cumulating event of the other (Centonze et al., 2010). In fact, synaptic defects, grey matter abnormalities, and demyelination have been found in selected CNS areas (i.e. the cortex, the hippocampus, the cerebral cortex, the thalamus, and the caudate-putamen) of MS patients at the earliest phases of the disease, also in the absence of infiltrating immune system cells (Bevan et al., 2018; Eshaghi et al., 2018). These neuronal alterations correlate with the dysregulation of the glutamatergic homeostasis and with the onset of neurological symptoms. In fact, the levels of glutamate in the cerebrospinal fluid and brain are higher in patients suffering from multiple sclerosis than in control individuals (Sarchielli et al., 2003; Srinivasan et al., 2005).

It is proposed that the glutamate receptors, and in particular the AMPA receptors, mediate the neurological events that sustain the progression of the disease, and therefore that their blockage could be beneficial to the pathology (Pitt et al., 2000; Smith et al., 2000; Werner et al., 2000). Most of the preclinical studies have been conducted on mice suffering from the experimental autoimmune encephalomyelitis (the EAE mice). These animals, besides central inflammation and demyelination also develop altered glutamatergic transmission within CNS. The treatment with an AMPAR antagonist (i.e. NBQX) reduces the neurological deficits in EAE mice by ameliorating the clinical scores, reducing axonal lesions, and increasing the survival of the oligodendrocytes (Pitt et al., 2000; Smith et al., 2000; Groom et al., 2003). In

fact, elevated extracellular glutamate levels can induce the death of neurons and oligodendrocytes (Mcdonald et al., 1998). It has been also proposed that the NBQX partially recover the clinical symptoms of EAE not only because it blocks the AMPA receptor present on neurons and oligodendrocytes but also because it blocks the AMPA receptors present on T cells (Ganor et al., 2003; Kanwar et al., 2004). In fact, an interesting study demonstrated that normal human T cells, human T leukemia cells, and mouse anti-myelin basic protein T cells highly express GluA3-containing receptors (Ganor et al., 2003). The excessive release of glutamate triggers the activation of the GluA3 subunit on T cells, which drives the CXCR4-mediated T cell chemotactic migration toward the site of the release of the chemokine CXCL12 in the central inflammation loci. Therefore, blocking AMPA receptors not only reduces axonal lesions and increases the survival of oligodendrocytes but also reduces the T-cell mediated damage in the CNS. Accordingly, Sarchielli and colleagues in 2007 found that both the mRNA and the GluA3 subunit are expressed on T cells of control and MS patients and that the expression of the GluA3 subunit is increased during relapses and in presence of active demyelinating lesions (Sarchielli et al., 2007). Thus, they confirmed that the activation of the GluA3 subunit enhances the proliferation and the chemotactic migration of T lymphocytes in both controls and MS patients

Interestingly, in mice suffering from EAE between 20 and 30 days post immunization, the early gene Arc/Arg3.1, which facilitates the removal of AMPA receptors from the plasma membrane (Chowdhury et al., 2006), was found to be dramatically downregulated in the striatum (Centonze et al., 2009). The consequence of this event is the increased expression, phosphorylation, and activity of the AMPA receptors. In support of this hypothesis, a study unveils an increased immunostaining of GluA1 calcium-permeable subunit in oligodendrocytes of the active lesion of MS patients respect to control tissue, whereas no changes were found in the expression of calcium impermeable GluA2-containing receptor

(Newcombe et al., 2008). Thus, the GluA1 up-regulation in oligodendrocytes may render these cells more vulnerable to the AMPA-mediated exocytotic events, resulting in calcium-mediated cell death.

Notably, a recent study provides evidence that the calcium influx in oligodendrocytes is primarily mediated by the activation of AMPA receptors and that the genetic deletion of the GluA4 subunit on mature oligodendrocytes decreases calcium responses (Evonuk et al., 2020). The selective mutation diminishes the clinical severity in the chronic phases of EAE by providing specific protection of the myelinated axons from the EAE injury, thereby reducing the myelin damage and the axonal loss (Evonuk et al., 2020). Interestingly, Bannerman et al., in 2007, demonstrated that the global deletion of the GluA3 subunits on oligodendrocytes reduces the AMPA receptor-mediated currents making these cells more resistant to excitotoxicity. They also found that the mice lacking the Gria3 gene, which encodes for the GluA3 subunit, when immunized with myelin oligodendrocytes 35-55 protein (MOG35-55), develop milder spinal demyelination.

All these observations support the hypothesis that calcium-permeable AMPA receptors expressed on oligodendrocytes contribute significantly to the axonal loss and demyelination in EAE and that the blockage or deletion of these receptors ameliorates the clinical picture.

Therefore, AMPA receptors might represent a valuable target to contrast the neuronal alterations and the severity of the symptoms of multiple sclerosis.

Nowadays, the approved disease-modifying therapies (DMTs) for multiple sclerosis target the inflammatory processes. Interestingly, the production of anti-AMPA autoantibodies represents a side effect of the therapy used in MS. DMTs can be divided into two categories. The first one includes the oral and injectable medications typically used as the first-line treatment. The second category is represented by the monoclonal antibodies, which are more efficacious in the treatment of MS but carry a higher risk of developing adverse effects.

Originally used in oncology, hematology, and transplantation medicine, alemtuzumab, a humanized monoclonal antibody, was introduced in 1991 for the treatment of patients with secondary progressive MS (Moreau et al., 1994), and it is now approved for the treatment of RRMS as second-line therapy.

The monoclonal antibody binds the CD52 glycoproteins expressed on lymphocytes, monocytes, macrophages, eosinophils, and dendritic cells (Buggins et al., 2002; Ratzinger et al., 2003). The binding between alemtuzumab and CD52 targets the cells for destruction, resulting in a selective depletion of the number of circulating B-cells and T-cells (Mone et al., 2006; Klotz et al., 2012)

The adverse effects of using this monoclonal antibody can occur up to five years and mainly correlate with autoimmune events, including thyroid disease (predominantly Graves' disease), immune thrombocytopenic purpura, renal disease, and rare cases of sarcoidosis and pneumonitis (Katsavos and Coles, 2018). Recently two cases of secondary autoimmune encephalopathy developed after the second alemtuzumab infusion cycles (Buscarinu et al., 2019; Giarola et al., 2019). In both cases, the patients are women affected by RRMS, which presented other well-known alemtuzumab-associated autoimmune complications (such as immune thrombocytopenic purpura and autoimmune hypothyroidism). The case reported by Giarola and colleagues was typified by autoimmune encephalitis manifesting as a polymorphic epilepsia partialis continua and status epilepticus. (Giarola et al., 2019). Interestingly, Buscarinu and co-workers reported the cases of a woman that, after the second cycle of treatment with alemtuzumab, presented progressive aphasia and an MRI pattern compatible with encephalitis (Buscarinu et al., 2019). After the hospitalization, the neurological status of the patient got worse, displaying anomic aphasia, motor apraxia, and a few days after, focal epilepsy with clonic movements and worse working memory. For this reason, she was treated with an antiepileptic drug, which stopped the seizures and ameliorated the neurological status.

However, twenty days after, her cognitive functions worsened again. The analysis of the CSF and the serum unveiled a high titer of antibodies direct against the GluA3 peptide A and B, which are common in patients with different types of epilepsy. Therefore, the patients started the immunoglobulin treatment, which ameliorated her neurological condition sustaining the possibility of alemtuzumab-associated autoimmune encephalitis involving, also, antibodies direct against the AMPA receptors (Buscarinu et al., 2019).

3.2 AMPA receptors and immune-stress-related disorders

Our modern life is shaped and even governed by stressful events. The body can sustain incredible amounts of stress, which makes it able to respond to life-threatening situations.

Stress differently affects learning and memory processes depending on the time and duration of the exposure, the type of stressor stimulus and the individual's ability to cope with stress, such as early life experiences, gender, or personality traits. For some people, stress can be good, which means excitement and challenge (acute stress). The effects induced by acute stress are preferentially discussed as adaptive responses to stress, which mainly improves working memory processes both in rodents (Yuen et al., 2009, 2011) and humans (Lupien et al., 2002; Smeets et al., 2006). Conversely, chronic stressful events can lead to a dysregulation of the ability of the organism to cope with stress then increasing the risk to develop stress-related disorders such as cardiovascular and metabolic diseases (Tamashiro et al., 2011; Simas et al., 2018), psychiatric and neurologic disorders (Lupien et al., 2018) or cancer (Cohen et al., 2007; Scrivo et al., 2011). Particularly, stress is considered the principal environmental risk factor for neuropsychiatric disorders such as depression, anxiety and mood disorders. These pathologies, and more in general stress-related disorders, are characterized by a dysregulation of the balance between the excitatory and inhibitory transmission, in addition to an chronic inflammation state (Berk et al., 2013; Liu et al., 2017; Jones et al., 2020). Interestingly, in the recent years several evidence point out that a cytokines can directly modulate the glutamatergic transmission (Viviani et al., 2003, 2006, 2014a; Pickering et al., 2005; Centonze et al., 2009; Di Filippo et al., 2013; Vezzani and Viviani, 2015; Stampanoni Bassi et al., 2019; Bruno et al., 2020), then contributing to the pathology.

3.2.1 Chronic stress as a disrupter of immune and neurochemical homeostasis

The concept of stress was first described by Hans Selye in 1936 as a non-specific reaction of the organism to a stimulus (Selye, 1936). He postulated the "general adaptation syndrome", which represents the physiological response mediated by the activation of both the sympathetic and neuroendocrine system (i.e. the hypothalamic-pituitary-adrenal (HPA) axis) that he observed in the rat following an acute non-specific stimulus. The general adaptation syndrome can be divided into three phases. Initially, in the first phase, the organism perceives the stimulus as a new condition and reacts promoting the activation of the sympathetic nervous system, which releases catecholamines responsible for the increase of blood pressure, muscular tone, and mobilization of energy. ("fight or flight" response, Cannon and De la Paz, 1911). The second phase is characterized by the attempt of the organism to resist stress by activating neuroendocrine systems and to restore the homeostasis. This is the property of the body to keep internal conditions stable and relatively constant over time. Finally, in the third phase, if stress persists, the organism continuously releases chemical mediators becoming unable to overcome the threat leading to deleterious effects (Marin et al., 2011; Mariotti, 2015; Vyas et al., 2016). This is why, the property of the organism to maintain a constant equilibrium in response to stress (homeostasis), has been revalued by Sterling and Eyer (1988) whose introduced the new concept of "allostasis" (*allos*, "other" and *stasis, "*remain still*"*). Allostasis is the adaptive process through which homeostasis is maintained by constant, fine changes in physiology (Sterling and Eyer, 1988). Thus, the body subtly alters, rather than maintains, its physiological parameter, including blood pressure and energy mobilization, to appropriately respond to challenging situations. Nevertheless, all these processes are energetically costly. The cumulative price that the organism pays for adapting to adverse situations by reaching a new equilibrium is the "allostatic load" (McEwen, 2000). Therefore, the "general adaptation

syndrome" described by Selye is the result of a process leading to the allostatic state, where the activation of the neuroendocrine system (i.e. HPA axis) promotes the adaptation to the stressor stimulus. When the stress response is sustained, the allostasis is followed by the allostatic load, which leads to pathophysiologic changes in the organism.

Nowadays, there is a clear distinction between two types of stress, acute and chronic stress. Acute stress can be beneficial for survival while chronic stressful events can cause a dysregulation of the ability of the organism to cope with them, leading to maladaptive responses, and thus to a higher vulnerability to neuropsychiatric, neurodegenerative, autoimmune, metabolic and cardiovascular diseases (Marin et al., 2011; Mariotti, 2015; Vyas et al., 2016). Chronic stress, in fact, profoundly alters the cognitive functions of the hippocampus (McEwen, 2001, 2007) and prefrontal cortex both in rodents (Cerqueira et al., 2005) and in humans (Young et al., 1999; Liston et al., 2009). In this context, it is important to highlight the main role played by the activation of the HPA axis during the response to adverse situations. When a stressor is perceived, the parvocellular neurons in the paraventricular nucleus (PVN) of the hypothalamus promote the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (APV; Calogero et al., 1992). The CRH and APV released from the hypothalamus act on the corticotropic cells of the anterior pituitary to induce the secretion of pro-opiomelanocortin (POMC), which is cleaved into adrenocorticotropic hormone (ACTH) and others bioactive peptides. The ACTH, in turn, stimulates the adrenal cortex to secrete glucocorticoids (corticosterone in rodents and cortisol in humans). Normally the release of glucocorticoids varies during the day, but after exposure to a stress stimulus, it dramatically increases.

Glucocorticoids are the final actors of the stress response and exert their action by binding two specific receptors: the mineralocorticoids receptors (MR) and the glucocorticoids receptors (GR; Reul and De Kloet, 1985). These two are ubiquitously expressed in the body,

and particularly in the corticolimbic structures, such as the hippocampus, prefrontal cortex, and amygdala (Herman et al., 1989), which are critically involved in stress responses. These receptors are also expressed on immune cells (Roszman and Brooks, 1997), and are well-known for exerting immunosuppressive and anti-inflammatory responses (Sorrells et al., 2009). However, evidence have proved that their activation following a danger signals also have a proinflammatory effects (Elenkov, 2008; Busillo et al., 2011)

Mineralocorticoid receptors has a higher affinity for glucocorticoids compared to GR. This means that at basal levels the mineralocorticoid receptors are activated, whereas the glucocorticoid receptors are only activated when the levels of corticosteroid hormones reach certain levels during the circadian peak or after stressful events (de Kloet et al., 2005; Herman et al., 2016). Glucocorticoids, together with noradrenaline and other neuromodulators, act in concert to regulate learning and memory processes and to facilitate the adaption of the body to stressor stimuli. By activating mineralocorticoid receptors, they modulate the response selection during learning processes (Oitzl and de Kloet, 1992; Sandi and Rose, 1994). Accordingly, the genetic deletion of MRs in the brain determines a cognitive decline (Berger et al., 2006). Differently, the activation of glucocorticoid receptors promotes the long-lasting consolidation of memory processes (Sandi and Rose, 1994), and affect the development and the function of the immune system (McEwen, 1998; Oppong and Cato, 2015; Cain and Cidlowski, 2017). The prolonged exposure to stressful events alters glucocorticoid receptor expression and causes anatomical and structural changes within different brain regions including the hippocampus, amygdala, and prefrontal cortex (McEwen, 1999, 2004; Sousa and Almeida, 2012). Accordingly, a week of stress (Brown et al., 2005) or just a single stress exposure (Izquierdo et al., 2006) has been shown to determine neuronal structural changes in the prefrontal cortex. This region presents a large expression of glucocorticoid receptors that make it particularly sensitive to stress. Indeed, it regulates thoughts, actions, mood, and

emotion in addition to playing an important role in the neural circuit for working memory (Goldman-Rakic, 1995; Arnsten, 2009). Impaired functions of the prefrontal cortex are critically involved in the development of several neuropsychiatric disorders such as schizophrenia, bipolar disorders and post-traumatic stress disorders (Hains and Arnsten, 2008; Goto et al., 2010; Sakurai and Gamo, 2019). Also, the amygdala emerged as a key region for modulating and regulating the stress responses by activating the HPA axis. The central nucleus of the amygdala is in connection with the noradrenergic centers of the brain, which activate the HPA axis. The amygdala projects also on the GABAergic neurons, which negatively control the activity of the CRH neurons. The stimulation of the amygdala activates the HPA axis by inhibiting the GABAergic neurons (Herman et al., 2003, 2005). Conversely, the activation of the hippocampus suppresses the function of the HPA axis (Dunn and Orr, 1984). This region, which have the highest expression of receptors for glucocorticoids (McEwen et al., 1968), is involved in learning and memory, emotions, and adaptation processes. The stress hormones, by binding their respective receptors in the hippocampus, trigger a mechanism of negative feedback regulation of the HPA axis determining the reduction of the release of glucocorticoids. This mechanism involves the excitatory hippocampal pyramidal neurons, which project on GABAergic interneurons expressed in the hypothalamic and striatum regions. The consequence is the inhibition of the PVN and thus of the HPA axis (Herman et al., 2005). The hippocampus, therefore, represents an important region for the regulation of stress responses by exerting functions that ensure the integrative role of the brain in the well-being of the organism. Thus, it is not surprising, that most mental and neurological diseases are associated with alterations of the hippocampus (Bartsch and Wulff, 2015; Gulyaeva, 2018).

This region is composed of a dorsal and ventral portion. The dorsal hippocampus is involved in learning and memory processes and in particular, in spatial memory (Maguire et al., 1997), while the ventral hippocampus is linked to emotional behavior and regulation of the

HPA axis (Fanselow and Dong, 2010). Thereby, the dorsal hippocampus is mainly studied for its involvement in neurodegeneration and dementia, while the neuronal circuitry and stress-induced signal of the ventral hippocampus are studied for their association with stress responses, depression, and other psychiatric disorders. The ventral hippocampus, in fact, is tightly linked to that brain region mainly involved in the modulation of anxiety, mood, and social behavior, such as the amygdala and prefrontal cortex (Belujon and Grace, 2011).

The neuronal circuitries of the corticolimbic regions described above are predisposed to modifications and reorganizations of the structure and activity (synaptic plasticity) during life, resulting in brain adaptation. Excessive or inappropriate synaptic excitability has been proposed to be a common feature of stress disorders and anxiety (Swanson et al., 2005; Chaouloff and Groc, 2011; Timmermans et al., 2013). Several preclinical studies have suggested that both acute and chronic stress induce changes in the basal glutamate release (Bagley and Moghaddam, 1997; Moghaddam, 2002; Yuen et al., 2009; Popoli et al., 2012). Accordingly, an increase of the level of extracellular glutamate has been observed after the exposure of rats to acute stress in the prefrontal cortex and also in the CA1 region of the hippocampus after the administration of peripheral corticosterone (Moghaddam, 1993; Venero and Borrell, 1999). Even chronic stress, by inducing the release of high amount of glucocorticoids, affects the regulation of glutamatergic transmission in the limbic regions (Lowy et al., 1993).

The receptors of the glucocorticoids behave through both a nongenomic mechanism via classical cell signaling pathway, and a genomic mechanism acting as transcription factors. *In vitro* studies have shown an increased excitatory transmission in the hippocampus due to the non-genomic effects mediated by the activation of the membrane mineralocorticoids receptors (Karst and Joëls, 2005; de Kloet et al., 2008). The corticosteroid hormones, moreover, positively regulate the glutamatergic transmission in the hippocampus through genomic effects

mediated by MRs (Wang and Wang, 2009; Chatterjee and Sikdar, 2014). The activation of MRs increases LTP, whereas the stimulation of GRs decreases LTP promoting LTD (Pavlides et al., 1995). Thus, since during chronic stress the levels of glucocorticoids are elevated, the low-affinity GRs are activated, leading to LTP impairments (McEwen and Sapolsky, 1995). The blockage of these receptors in the hippocampus and prefrontal cortex has been shown to prevent stress-triggered LTP dysregulation (Mailliet et al., 2008). Additionally, chronic stress reduces adult neurogenesis, causes dendritic atrophy of the hippocampus (McEwen, 1999) and decreases the reuptake of glutamate from the synaptic cleft both in the cortex and hippocampus (Yuan and Hou, 2015).

An important aspect of synaptic plasticity is the strictly controlled trafficking and synaptic targeting of the glutamate AMPA receptors. A growing body of preclinical evidence showed changes in the expression of AMPA receptors after chronic stress exposure, although conflicting results were obtained depending on the stress protocol, the species, and the brain area explored. It has been found that chronic social stress provokes in male vulnerable mice a reduced mRNA expression of the AMPA receptor subunits GluA1 and an increased mRNA expression of the GluA2 subunits in the hippocampal CA1 region and dentate gyrus compared to resilient rats (Schmidt et al., 2010). A reduced expression of GluA1 subunits in the hippocampus, but not of GluA2, has been also found in male rats after the exposure to chronic unpredictable stress (CUS) for 3 weeks (Kallarackal et al., 2013). Conversely, Yu and colleagues, applying almost the same stress protocol as the previous work, described a diminished mRNA expression of the GluA2 subunits in the hippocampus of male rats, which was restored with antidepressant treatment (Yu et al., 2014), while other authors didn't find any changes in the expression of GluA1 and GluA2 subunits in hippocampus of rats after the exposure to CUS for 3 weeks (Qin et al., 2004; Elhussiny et al., 2021).

Not only the hippocampus region has been investigated. For instance, it has been found a reduction of the expression of the GluA1 subunits in the prefrontal cortex of rat exposed to CUS, which was corrected by the treatment with the antidepressant ketamine (Li et al., 2011). Moreover, male rats that underwent both repeated unpredictable chronic stress and repeated restrain stress for 5 or 7 days, showed a reduced total level of GluA1 subunits as well as a reduction in the surface expression of both GluA1 and GluA2 subunits in the prefrontal cortex (Yuen et al., 2012). Interestingly, the reduction of the expression of the GluA subunits was reverted by the injection of GR antagonist, indicating that chronic stress downregulates AMPA receptors expression via GR activation (Yuen et al., 2012).

Another chronic stress protocol that is generally applied is the restrain stress. Also using this stress protocol emerge contrasting results (Schwendt and Ježová, 2000; Rosa et al., 2002; Yi et al., 2017). The differences that emerged in all these studies are probably due to different aspects including the typology and duration of the stress protocol, the experimental procedure, and the different breeding and handling of the animals. However, what is needed to be highlighted is that chronic stress dysregulates the excitatory synapses and the expression of AMPA receptors, which can be reverted by antidepressant treatments (Li et al., 2011; Yi et al., 2017), or by injection of GR antagonist (Yuen et al., 2012), giving rise to the important role played by these receptors in the maladaptation induced by stress.

Interestingly, a recent work highlighted a link between the proinflammatory cytokine IL-6 and AMPA receptors-mediated signaling at the post-synaptic level (Hettinger et al., 2018). Accordingly, treating antigen-induced arthritis rats with NBQX ameliorate the inflammatory state (Bonnet et al., 2015). Additionally, several findings support a role for TNF-α (tumor necrosis factor-alpha) in modulating the AMPA receptors signaling (Viviani et al., 2003, 2006; Pickering et al., 2005; Vezzani and Viviani, 2015). Moreover, in the recent years studies proved that lymphocyte T highly express GluA3 subunits (Ganor et al., 2003; Sarchielli et al., 2007).

Altogether these evidence suggested that the immune system is particularly involved the regulation of the glutamatergic transmission by affecting glutamate receptors signaling (Centonze et al., 2010; Di Filippo et al., 2013; Viviani et al., 2014a; Stampanoni Bassi et al., 2019; Bruno et al., 2020). Interestingly, increasing data indicate that alterations in the glutamatergic transmission observed in psychiatric stress-related disorders, such as mood disorders, schizophrenia and depression, can be partially mediated by the immune system (Chourbaji et al., 2006; Müller and Schwarz, 2007; Dantzer et al., 2008; Dantzer and Walker, 2014; Haroon et al., 2018).

It is well assumed that chronic stress inhibits the secretion of proinflammatory cytokines and activates anti-inflammatory responses leading to an immunosuppressive condition (Dhabhar and Mcewen, 1997; Reiche et al., 2004; Gouin, 2011; Dhabhar, 2014). This mechanism is regulated by glucocorticoids and catecholamines that by binding their respective receptors present on the immune cells downregulate the release of the proinflammatory cytokines such as IL-1 β, IL-6, TNF-α and IFN-γ (interferon-γ) and upregulated the secretion of the anti-inflammatory cytokines such as IL-4, IL-10 and IL-13 (Elenkov and Chrousos, 1999; Chrousos, 2000; Tracey, 2002). In addition, chronic stress can enhance Th1 to Th2 shift. Th1 cells primarily secrete the proinflammatory cytokines, which promote the cellular immunity, whereas the Th2 cells secrete the anti-inflammatory cytokines, which promote the humoral immunity (Chrousos, 2000; Webster et al., 2002; Elenkov, 2004; Reiche et al., 2004; Segerstrom and Miller, 2004; Xiang and Marshall, 2011). However, when the stress exposure is sustained for long period the glucocorticoid receptors are downregulated and therefore the capacity of the glucocorticoids to suppress the immune system declines (Webster et al., 2002; Miller et al., 2008; Cohen et al., 2012; Rohleder, 2012). Additionally, other mechanisms increase the secretion of proinflammatory cytokines inducing inflammatory responses, which culminate in various diseases. Several work have in fact demonstrated that

chronic stress, including job stress, low socioeconomic status, caregiver stress, childhood adversity and loneliness, increases proinflammatory cytokines release such as IL-6 and IFN-γ (Kiecolt-Glaser et al., 2003; Graham et al., 2006; Gouin et al., 2012). Other support came from studies demonstrating that lots of the individuals even show a depressive-like behavior (Glaser et al., 2003; Chourbaji et al., 2006; Raison et al., 2006; Dantzer et al., 2008). An interesting work have also pointed out that the different immune responses to stress could depend on the intraindividual ability to cope with the adverse events. Vulnerable rats are prone to secrete proinflammatory cytokines whereas resilient rats display a suppression of the inflammatory process (Wood et al., 2015). Thus, the duration and intensity of stressor and the individual differences can differently affect the cells of the immune system in modulating the secretion of cytokines.

3.2.2 Early life stress programming: the perinatal stress rat as a model of disruption of glutamatergic and neuroimmune homeostasis

The mechanism by which nature (gene) and nurture (environmental stimuli) influence each other is relevant to understand the risk of individuals developing stress-related disorders, such as anxiety and depression. The individuals' differences in vulnerability to display chronic disease may be programmed by early life events, including the fetal growth in utero. During this critical period, oxygen and nutrient are essential for the fetal growth. If they lack, the fetus triggers adaptive mechanisms to sustain its development. The consequence of this adaptation is small body size at birth, which has been also linked with cardiovascular diseases (Barker and Osmond, 1986; Barker et al., 1993a). Moreover, the low birth weight has been associated with the development of diabetes and hypertension in humans (Barker et al., 1990, 1993b) supporting the concept that early life is a critical period for shaping the lifelong health of an individual (Barker, 1995). In addition to clinical evidence, also preclinical studies demonstrated that low intrauterine nutrition predisposes to metabolic, endocrine, or immune abnormalities (Barker and Clark, 1997), which can persist all life-long. These observations led to the elaboration of the theory of Developmental Origins of Health and Disease (DOHaD), which is corroborate by studies conducted in the past two decades in human as well as in animals (Nemeroff, 2004; Seckl, 2007; Maccari et al., 2017).

Besides malnutrition, also stress and stress hormones can program changes in the fetal development. Notably, glucocorticoids are important for embryonal growth, promoting cellular differentiation and fetal lung maturation (Ward, 1994; Garbrecht et al., 2006). They are also crucial for the development of other organs including the brain, kidney, pituitary, and thyroid (Fowden et al., 1998).

Glucocorticoids normally increase during pregnancy and cross the placenta, but the enzyme 11β-HSD2 (11-β-hydroxysteroid dehydrogenase 2) protects the fetus from the maternal glucocorticoids by inactivating them. However, the barrier allows the passage of 10-20 % of maternal glucocorticoids. Inappropriate, probably due to chronic maternal stress, or premature exposure of the fetus to excessive levels of glucocorticoids can determine alterations of the normal development resulting in impaired physiological function during life (Moisiadis and Matthews, 2014). Accordingly, prenatal exposure to synthetic glucocorticoids causes the reduction of weight at birth (Benediktsson et al., 1993), and metabolic and affective disorders in adulthood (Seckl, 2004) profoundly modifying the regulation of the HPA axis. Also the reduced level of the enzyme 11β-HSD2 correlates with small body size at birth and hypertension in adulthood both in humans (Lindsay et al., 1996; Murphy et al., 2002) and rodents (Holmes et al., 2006).

Not only the intrauterine period, however, is critical for the programming but also the maternal care in the early days after birth. Several studies in rodents address the role of maternal care, measured as licking, grooming, and arched-back nursing in programming stress responses and HPA axis in the offspring (Liu et al., 1997; Meaney, 2004). Variations of maternal care have been in fact associated with the different behavioral responses to stress such as anxiety-like behavior or fear (Caldji et al., 1998). Interestingly, the altered phenotype observed in the early life stressed rats is reverted when they were adopted by the mother not stressed (Maccari et al., 1995). The adaption arises the maternal behavior and reduces the secretion peak of corticosterone observed in the adult stressed offspring (Maccari et al., 1995).

The development of epigenetics studies allows the comprehension of the long-lasting mechanism of early programming. Epigenetic modifications are defined as changes in a chromosome but not in the DNA molecule itself, exerting lasting control over gene expression and mediating stable alterations in brain functions. The classical alteration is the methylenation

of the DNA (Hotchkiss, 1948), which is associated with the silencing of gene transcription. The acetylation at specific lysine sites, on contrary, determines the activation of gene transcription (Zhang and Meaney, 2009). For instance, it has been demonstrated that increased maternal behavior produces stable changes in DNA methylation and chromatin structure (Weaver et al., 2004), causing elevated transcription of the glucocorticoid receptor gene (Meaney and Szyf, 2005). Several other evidence during the year supported the hypothesis that early life events cause epigenetic modification and in particular DNA methylation (Weaver et al., 2007; McGowan et al., 2008, 2009, 2011; Oberlander et al., 2008; Provençal et al., 2012; Klengel et al., 2013; Li et al., 2020; Juruena et al., 2021).

All the significant progresses in understanding the effects and the programming induced by early life stress, such as the epigenetic studies, were made possible thanks to the different developed animal models, since investigating early environmental changes in human results very difficult to perform. To be considered applicable, an animal model have to respect three criteria of validities (Willner, 1984; Berton et al., 2012). The first is construct validity, which refers to replicating the etiologic causes that are responsible for human disease. The second criterium is represented by face validity, which indicates that the animal model has to present similar features including behavioral, anatomical, neuropathological, or biochemical analogy with that observed in human disease. Finally, the third criterium is the predictive validity that indicates that the animal model reacts to pharmacological treatments similarly to humans. The choice of a suitable animal model is essential for translational research and for investigating new candidates for the treatment of pathologies.

Seymour Levine in 1957 developed the neonatal handling paradigm, which consists of 15 minutes of daily maternal separation of pups as a litter from postnatal day 1 (PND1) to PND 21 (Levine, 1957). Subsequently, a model of maternal separation consisting of the daily separation of the pups from the mother for 3 hours up to 6 between PND1 to PND14 was set

up by Plotsky and Meaney (Plotsky and Meaney, 1993). Another model of postnatal adversity is the model of maternal separation with early weaning (Laban et al., 1995; George et al., 2010). This paradigm consists of separating the mothers from the pups every day for 3 hours from PND2 to PND17 followed by early weaning at PND17 (George et al., 2010). Another interesting model of postnatal handlings is maternal deprivation, which, as the name suggests, consists of depriving the pups of their mother for 24 hours, usually on PND9 (Roceri et al., 2002; Viviani et al., 2014b). Early handlings enhanced the active maternal behaviors measured as licking, grooming, and arched back nursing, and reduces the HPA axis responses to stress resulting in stress resilience in the adult offspring (Meaney et al., 1996; Pryce et al., 2001). Conversely, prolonged separation coupled with poor maternal care produces more stress vulnerable organisms (Levine, 2005). Thereby, another paradigm to study the postnatal environmental alterations consists in separating mothers that display low and high maternal care (Liu et al., 1997; Champagne et al., 2003; Weaver et al., 2004). However, not only the postnatal early life stress model has been developed. Indeed, several prenatal animal models have been set up including hormonal manipulation, undernutrition, infection, drug intake, and physical stress (Braun and Bock, 2011; Muhammad and Kolb, 2011; Mychasiuk et al., 2011; Suenaga et al., 2012; Xu et al., 2013; Tartaglione et al., 2020). These animal models are used to better characterize the long-term behavioral and neuroendocrine alterations observed in the stress-induced disorders. Accordingly, a model of prenatal social stress has been developed by Brunton and Russell (Brunton and Russell, 2010). Their model consists of transferring a pregnant dam into the cage of an unfamiliar lactating mother for 10 min per day in the last week of pregnancy. This procedure causes social stress to the pregnant dam, which in turn causes long-lasting effects on the development of the offspring (Brunton and Russell, 2010; Brunton et al., 2013). Another very interesting model to study the long-term effects of early life stress is the perinatal stress rat model, which has been set up by Stefania Maccari (Maccari

et al., 1995, 2003; Morley-Fletcher et al., 2003; Marrocco et al., 2012, 2014; Mairesse et al., 2015; Reynaert et al., 2016). Here, the pregnant rats are exposed to restrain stress from the eleventh day of pregnancy until the birth of the offspring. The restrain procedure consists of placing the pregnant dams for 45 minutes for three sections per day (at 9 am, 12 am, and 3 pm) in a Plexiglas cylinder under bright light. At birth, the offspring are left undisturbed with their mothers. The offspring of the stressed mothers are continuously exposed to stress also in the postnatal period due to inadequate maternal care. Indeed, mothers that have been submitted to restrain stress show lower maternal care compared to unstressed mothers. Therefore, this procedure combines both prenatal stress and postnatal stress, and for this reason is defined as perinatal stress (PRS).

As discussed above, chronic stress during pregnancy increases the level of glucocorticoids, which cross the placenta. As well, the PRS procedure enhances the level of corticosterone in the pregnant dams. The consequence is that the early exposure of the fetus to a high concentration of glucocorticoids programs long-lasting behavioral and biochemical changes. Multiple studies, in fact, found that exposure to a high level of corticosteroid hormones in early life can adversely program the HPA axis increasing the vulnerability to develop metabolic, inflammatory, neuropsychiatric, and neurodegenerative disorders (Harris and Seckl, 2011; Moisiadis and Matthews, 2014; Hoeijmakers et al., 2015; Chen and Baram, 2016; Elwenspoek et al., 2017). Moreover, clinical and preclinical studies demonstrated that stressful experiences in the early phase of the development can cause persistent changes in the ability of the HPA axis to respond to stress (Glover and O'Connor, 2002; Seckl and Meaney, 2004). Accordingly, PRS causes enhanced stress-induced glucocorticoid release in pre-weaning rats and prolonged secretion of corticosterone after stress exposure in both adult and aged rats (Henry et al., 1994; Vallée et al., 1999). The alteration of the endocrine system is associated with a profound fragmentations of sleep architecture and disruption of circadian

rhythms (Dugovic et al., 1999; Mairesse et al., 2013). A possible mechanism of the altered regulation of the HPA axis has been proposed to be the decreased expression and activation of the glucocorticoid receptors in the hippocampus of PRS and in turn, the impaired glucocorticoid negative feedback (Henry et al., 1994; Maccari et al., 1995; Morley-Fletcher et al., 2003, 2018; Van Waes et al., 2006).

Several lines of evidence suggest that the increased levels of glucocorticoids observed following stress, cause changes in the glutamatergic transmission via MRs and GRs activation, influencing cognitive and emotional processes. (Karst and Joëls, 2005; de Kloet et al., 2008, Lowy et al., 1993). The altered glutamatergic neurotransmission has been increasingly associated with the development of stress-related mental disorders (Popoli et al., 2012). The PRS decreases the release of glutamate from the ventral hippocampus, which is mainly related to stress and emotions, but not from the dorsal hippocampus in adult male rats (Marrocco et al., 2012). Interestingly, the spontaneous release of glutamate in PRS rats was not affected, suggesting that the alteration in the exocytosis of glutamate may involve the presynaptic exocytotic machinery. The core of the presynaptic machinery responsible for the vesicular neurotransmitter release, including glutamate, is composed of SM (Sec1/Munc18-like) proteins and SNARE (Soluble NSF Attachment Receptor Protein) complex, which in turn is composed of vesicular proteins (synaptobrevin 1 or 2) and synaptic membrane proteins (syntaxin 1 or 2 and SNAP 25). SNARE and SM proteins mediate the fusion of synaptic vesicles with the presynaptic membranes ensuring the release of the neurotransmitter (Lang and Jahn, 2008; Rizo and Rosenmund, 2008; Südhof and Rothman, 2009). Indeed, the abnormalities in the exocytosis of glutamate observed in the perinatal stress rat model reflect the selective reduction of the synaptic vesicle-associated proteins found in the ventral hippocampus of adult male offspring (Marrocco et al., 2012).

Besides the disruption of glutamate release and synaptic machinery, PRS induces alterations of the density of the glutamatergic metabotropic receptors in the ventral hippocampus. It has been demonstrated a reduction of mGlu1 in adult males but not females (Van Waes et al., 2009), and of mGlu5 selectively in adult (Zuena et al., 2008) and aged male rats (Gatta et al., 2018) as well as in pups at PND 14 and PND 22 (Laloux et al., 2012). The second group of metabotropic receptors has been also found to be altered by early life stress. In the ventral hippocampus, mGlu2/3 receptors are decreased in PRS pups at PND22 (Laloux et al., 2012) as well as in adult PRS rats of both sexes (Zuena et al., 2008). The mGlu2 and mGlu3 transcripts and protein density have been also found reduced in the frontal cortex of adult male mice exposed to prenatal stress (Matrisciano et al., 2013). Hence, these outcomes suggest that PRS induces glutamatergic alteration across the life span.

Additionally to the functional alterations, early life stress induces also long-lasting changes in the behavioral performance. For instance, PRS male rats show a reduced social playing during adolescence (Morley-Fletcher et al., 2003), increased behavioral responses to social isolation in infancy (Laloux et al., 2012), and increased immobility time in the forced swim test (Morley-Fletcher et al., 2011; Van Waes et al., 2011). They also display a reduced risk-taking behavior as highlighted by the less time spent in the open arm of the elevated-plus maze (Vallée et al., 1997; Zuena et al., 2008; Marrocco et al., 2012) and in the light compartment of the light-dark box (Marrocco et al., 2012). These behavioral alterations are consistent with the evidence showing that the early life adverse events represent an environmental risk factor for developing stress-related disorders such as anxiety and depression (Shea et al., 2005; Lopez-Duran et al., 2009; Guerry and Hastings, 2011; Du and Pang, 2015). Remarkably, PRS females display a different pattern in the behavioral test. They show increased time spent in the open arm of the elevated plus maze with respect to control. Therefore, the opposite behavioral profile and the different neurobiological parameters

observed between males and females (Zuena et al., 2008; Van Waes et al., 2009; Laloux et al., 2012; Gatta et al., 2018), suggest a sex dimorphic profile induced by PRS, in which females seem to be protected against early life stress, while male are more vulnerable.

Additionally, the altered risk-taking behavior observed in male rats exposed to early life stress is causally related to the decreased glutamate release from the ventral hippocampus, given that the pharmacological intrahippocampal injection of mGlu2/3 and $GABA_B$ receptor antagonist, which favored the release of glutamate, reverted their anxiety-like behavior (Marrocco et al., 2012).Thus, this evidence supports the hypothesis that glutamatergic transmission is directly implicated in the endocrine and behavioral alterations triggered by PRS.

Another important feature of the PRS rats is the anticipated aging process. Aging is characterized by a progressive deterioration of physiological integrity. As we age, the hippocampal neurogenesis is reduced, the synaptic plasticity decreased and the inflammatory state augmented, similarly to what it is observed in PRS rats. For instance, male rats prenatally stressed present a deficit in hippocampal neurogenesis (Lemaire et al., 2000), altered social memory, disrupted synaptic plasticity (Brunson et al., 2005; Marrocco et al., 2012, 2014) and increased inflammatory response (Vanbesien-Mailliot et al., 2007). Several others studies find out that early life stress induces accelerated aging both in human and animals (Entringer et al., 2011, 2012; Danese and McEwen, 2012; Heidinger et al., 2012; Price et al., 2013; Haapanen et al., 2018; Marrocco et al., 2020). Particularly, early life adverse events engender an increased level of the typical markers of the inflammation such as white blood cell count, circulating proinflammatory cytokines and CRP (C-reactive protein). Accordingly, it has been found an association between childhood adverse events and augmented white blood cell counts (Surtees et al., 2003). Others work found increased level of proinflammatory cytokines such as IL-1β, IL-6 and TNF-α, and CRP in individuals that experienced childhood adversity (Danese and

McEwen, 2012; Baumeister et al., 2016). Also preclinical studies highlighted alterations of the immune responses engender by early life stress. For instance, it has been found that maternal separation increased the levels of IL-6 in the hippocampus of the offspring (Banqueri et al., 2019) and of TNF-α and IL-1 (do Prado et al., 2016; Roque et al., 2016) . Increased level of IL-6 has been found also in rats exposed to perinatal restrain stress (Zhang et al., 2016). In addition, PRS induces decreased sex hormone levels in both adult and middle-age rats of both sexes (Reynaert et al., 2016; Van Camp et al., 2018), supporting the idea that the early life stress induced anticipated aging.

3.2.2.1 Interventional strategies to correct PRS-induced abnormalities in glutamatergic transmission: antidepressants and ampakine

The PRS rats model recapitulates the hallmarks of stress-related disorders including anxiety and depression. This model, in fact, displays prolonged secretion of corticosterone after stress, a persistent deficit in hippocampal neurogenesis, and behavioral and neurochemical alterations that are consistent with anxiety and depressive phenotype (Dugovic et al., 1999; Darnaudéry and Maccari, 2008; Zuena et al., 2008; Maccari et al., 2017). Accordingly, Morley-Fletcher in 2011 has demonstrated that the chronic treatment of adult PRS rats with agomelatine, an antidepressant that behaves as MT1/MT2 melatonin receptor agonist and as 5-HT_{2C} receptor antagonist (de Bodinat et al., 2010), reverted the alterations induced by the early life exposure to stress. For instance, the agomelatine treatment increased neurogenesis in the ventral hippocampus and synaptic density of mGlu2/3 and mGlu5 receptors that were reduced by PRS (Morley-Fletcher et al., 2011). The antidepressant corrected also the behavioral phenotype induced by PRS. The immobility time observed in prenatally stressed male rats in

the forced swim test as well as the time spent in the open arm of the elevated-plus maze was normalized following the treatment (Morley-Fletcher et al., 2011).

In 2012 Marrocco and co-workers proved a causal link between risk-taking behavior and the reduced release of glutamate from the ventral hippocampus of PRS rats. Conversely, no changes were found in the GABA release (Marrocco et al., 2012). Thus, PRS rats display a disrupted balance between excitatory and inhibitory transmission. The imbalance between glutamate and GABA has been shown to be implicated in memory impairment, anxiety, and depressive disorders (Tordera et al., 2007; Chen et al., 2010). Several lines of evidence, in fact, suggested the importance of the role played by the glutamatergic transmission in the development of psychiatric disorders (Altamura et al., 1993; Javitt, 2004; Li et al., 2019). Thus, to support the glutamatergic hypothesis of stress-related disorders, Marrocco and colleagues in 2014 investigated the effects of two antidepressants on the glutamatergic transmission and behavioral phenotype of PRS rats chronically treated. Indeed, this model recapitulate the hallmarks of the stress-related disorders, and thereby, it can be considered as a good model to study the antidepressants drugs acting on the excitatory transmission. The antidepressants used in study were: i)fluoxetine, a selective serotonin reuptake inhibitor (SSRI) used for the treatment of major depression and ii) agomelatine, used for treating anxiety disorders.

What emerged from the study was that the three weeks of chronic treatment corrected the glutamatergic transmission as well as the altered emotional and cognitive behaviors induced by PRS. Accordingly, both the antidepressants increased the time spent in grooming in the splash test, increased social memory performance and decreased both the immobility time in the forced swim test and the latency to enter in light compartment of the light-dark box (Marrocco et al., 2014). Moreover, PRS rats pharmacologically treated displayed enhanced KCl-evoked glutamate release as a consequence of the increased expression of synaptic vesicle-associated proteins in the ventral hippocampus, including synapsin Ia/b and IIa,

VAMP, and Rab 3a (Marrocco et al., 2014). Thus, altogether these results confirmed that the impaired glutamatergic transmission lies at the core of the PRS rats.

The glutamatergic hypothesis of psychiatric disorders was further supported by the finding that the ketamine, an NMDA receptor non-competitive antagonist, shows a rapid efficacy in treating depressive disorders (Zarate et al., 2006; Li et al., 2010b; Duman et al., 2012; Murrough et al., 2013). The use of ketamine, however, is limited since it is associated with neurocognitive deficits in working and episodic memory, and also causes psychomimetic and dissociative effects (Short et al., 2018). Thus, the findings concerning the use of ketamine in treating depression encouraged further investigation into the efficacy of non-ketamine NMDA receptor antagonists (Newport et al., 2015). However, these agents were not so efficacious as ketamine. Subsequently, a growing body of evidence supported the crucial involvement of AMPA receptors in mediating the antidepressant effects of ketamine (Maeng et al., 2008; Koike and Chaki, 2014; Park et al., 2015). Accordingly, preclinical studies showed that the rapid and sustained antidepressant effects exerted by ketamine were absent when rodents are previously treated with the AMPA receptor antagonist NBQX (Maeng et al., 2008; Koike et al., 2011; Koike and Chaki, 2014; Zanos et al., 2016). It has been also shown that ketamine promotes the activation of AMPA receptors (Björkholm et al., 2015; El Iskandrani et al., 2015) and the upregulation of GluA1- and GluA2-containing receptors both in the prefrontal cortex and hippocampus (Li et al., 2010b; Nosyreva et al., 2013; Koike and Chaki, 2014; Yang et al., 2016; Zanos et al., 2016). Thus, these data indicate that the activation of AMPA receptors is required for the antidepressant action of ketamine. Such findings prompted the investigation of drugs that enhance the AMPA receptor-mediated signaling for their potential role in the treatment of depressive disorders. Accordingly, positive allosteric modulators (PAMs) of AMPA receptors, initially emerged for treating cognitive impairment and neurodegeneration, are nowadays studied as a cure for stress-related disorders.

In this context, rats parentally stressed have been chronically treated with S 47445 (Morley-Fletcher et al., 2018), a selective AMPA receptor potentiator that enhances neurogenesis, emotional and cognitive functions, and possesses neuroplasticity activities (Bretin et al., 2017; Calabrese et al., 2017; Mendez-David et al., 2017). The effects observed on the programming effect induced by PRS following the treatment with S 47445 were the same as that observed with the classic antidepressant, fluoxetine. The behavioral alterations that typified the PRS rats model, including the reduced risk-taking behavior in elevated plus maze and light-dark box test, the impaired social cognition in social memory, and the decreased self-care observed in the splash test, were all normalized by the chronic administration with the AMPA PAM (Morley-Fletcher et al., 2018). The same efficacy of S 47445 in the behavioral test was obtained also in mice chronically treated with corticosterone and in rats exposed to chronic mild stress (Mendez-David et al., 2017). These stress models, however, do not recapitulate the early programming of stress-related disorders.

Interestingly, it has been found that the chronic treatment with AMPA PAM normalized the impaired release of glutamate, and the reduced expression of mGlu5 and synaptic proteins (Munc-18, Rab 3a, and synapsin IIa) in the ventral hippocampus of PRS rats. The effect of S 47445 on the synaptic machinery, which is implicated in the trafficking of AMPA receptors, suggest a potential effect of PRS on AMPA receptors that need to be investigated.

Interestingly, the authors highlighted a direct correlation in the ventral hippocampus between the reduced exocytosis of glutamate and the low social memory performance as well as a negative correlation between the reduced glutamate release and the high latency to self-grooming that are both maintained following the treatment with the positive allosteric modulator of AMPA receptors (Morley-Fletcher et al., 2018).

AIMS OF THE THESIS

The AMPA receptor and its role in the synaptic glutamatergic transmission in both physiological and pathological conditions of the CNS represent the common thread of the research carried out during my PhD project. Particularly, I tried to tackle certain aspects of these receptors that are still unsolved or controversial.

In the **first chapter** I discuss the results obtained trying to elucidate the subunit composition of the receptors. By using the "immuno-pharmacological approach", which consists in the use of commercial antibodies direct against the amino-terminal sequence of targeted protein as pharmacological tools, I hypothesized the composition in subunits of naïve AMPA autoreceptors in the cortex of mice. Interestingly, beside deciphering the GluA subunit composition, the study also highlighted mechanisms of antibody-induced receptor re-distribution/trafficking in nerve endings that could have a key role in the development of neurological disorders.

I also asked whether the presence of the antigen-antibody complex at the outer side of the plasma membranes could represent a triggering stimulus for unusual activation of the complement system, which is an indirect event that could have a pathological significance in autoimmune diseases associated to the production of anti-GluA autoantibodies, including the Rasmussen's encephalitis (Rogers et al., 1994; Andrews et al., 1996) and some forms of frontotemporal dementia (Borroni et al., 2017). The study allowed to unveil both *complement-insensitive* and *complement-mediated* synaptic event that could have opposite outputs in the synaptic transmission and therefore in the course of autoimmune diseases. (van Coevorden-Hameete et al., 2014; Peng et al., 2015; Borroni et al., 2017).

In the **Chapter two**, I had the opportunity to take part to a study dedicated to evaluating the effect of the CSF of patients suffering from FTD titrated for anti-GluA on the release of glutamate. This part of my work is briefly summarized since the results were much more intricate than expected and need further detailed studies.

It is widely accepted that AMPA receptors are pivotal to synaptic plasticity and excitatory transmission representing therefore the preferential targets of deleterious signaling at the basis of stress-related disease (Citri and Malenka, 2008; Maccari et al., 2017; Forrest et al., 2018). Thanks to the doctoral agreement between the University of Genoa and the University of Lille, I had the opportunity to work in the Glycostress laboratory in Lille directed by Pr. S Morley-Fletcher. This laboratory is internationally recognized for the study of an animal model of early life stress, the perinatal restrain stress model, that has been developed by Pr. Stefania Maccari. The model recapitulates the hallmarks of stress-related disorders (Maccari et al., 2017) and allow to study the development of these signs during animal life. The PRS male rats are typified by a reduction of evoked-glutamate release and altered SNARE proteins expression in the hippocampus (Marrocco et al., 2012) , as well as by a reduced density of the metabotropic glutamate receptors mGlu2/3, mGlu5 and mGlu1 subtypes (Zuena et al., 2008; Laloux et al., 2012). These observations indicate that PRS rats display a profound impairment of glutamatergic transmission, which lie at the core of the pathological phenotype induced by PRS. The possibility that the glutamatergic impairment could affect also the expression and the membrane insertion of the AMPA receptors was not so far investigated, despite some recent data showing that positive allosteric modulator of the AMPA receptors can recover behavioral skills and molecular defects that typify the PRS rats (Morley-Fletcher et al., 2018). Based on these first observations, the **Chapter three** of my thesis was dedicated at evaluating whether and to what extent AMPA receptors are altered in PRS rats, paying particular attention to the biological sex and age-related modifications.

The thesis represents an honest and accurate report of all the results achieved within the three years of my PhD course and I do really hope that the outcomes obtained on the different topics improves our knowledge of the AMPA receptors and their role in the synaptic transmission and in selected central pathologies.

MATERIALS AND METHODS

1. Animals

1.1 C57BL/6J mice

Adult male C57BL/6J mice were purchased from Charles River (Calco, Italy). Animals were housed in the animal facility of DIFAR, Section of Pharmacology and Toxicology and kept at constant temperature (22°C) with a regular 12 h light/dark cycle (light-off at 7 pm) and with food and water freely available. Mice were euthanized by cervical dislocation, followed by decapitation, and the cortex rapidly removed. The experimental procedures were in accordance with the European legislation (European Communities Council Directive of 24 November 1986, 86/609/EEC) and the ARRIVE guidelines, and they were approved by the Local Committee for Animal care and welfare of the University of Genova and the Italian Ministry of Health (DDL 26/2014 and previous legislation; protocol number n° 75F11.N.IMY). All experiments followed the Guidelines for Animal Care and Use of the National Institutes of Health and are in accordance with the Society's Policies on the Use of Animals and Humans in Neuroscience Research. In line with the 3Rs rules (replacement, refinement and reduction), only the number of animals necessary to produce reliable results have been used.

1.2 Sprague-Dawley rats

Nulliparous female Sprague–Dawley rats, weighing approximately 250 g each, were purchased from Charles River (France) and housed in the animal facility of the University of

Lille. The animals were kept under standard conditions with a regular 12-h light/dark cycle and with food and water freely available. After two weeks of group housing (5 females for cage), each female was housed for one week with an experienced male. After mating, the females were individually housed. A gain of at least 10 g was considered an indication of pregnancy. After the PRS procedure (see stress procedure), behavioral and biochemical examinations of the ventral hippocampus of adult (3–5 months of age) male and female progeny were performed. The same outcome has been investigated also in the hippocampus (ventral and dorsal) and prefrontal cortex of aged (21-22 months of age) male and female offspring. The blood (plasma and serum) have been also collected in aged rats. Experiments were performed following the rules of the European Communities Council Direc tive 86/609/EEC. The Local Committee CEEA-75 (Comit´e d'Ethique en Experimentation Animale Nord-Pas de Calais, 75) approved the experimental.

2. Stress procedure

From day 11 of pregnancy the dams were randomly assigned to control or restrain stress group (15 per group). Control females were left undisturbed were handled once per week during body weight gain. The pregnant female of restrain stress group were subjected from the day 11 of pregnancy until the deliver three restrain stress sessions lasting 45 min each. During each session the dams were placed in a transparent plastic cylinder and exposed to bright light. PRS, i.e., the offspring of dams exposed to restrain stress causing reduced maternal care, were obtained according to our standard protocol (Maccari et al., 1995). Offspring was weaned 21 days after birth, housed in groups of two or three and maintained under standard conditions and left undisturbed until the beginning of the experiments. Only

male and female offspring from litters with a balanced sex ratio were used for the experiments.

3. Analysis of maternal behavior

Control and restrain stressed dams were placed individually in standard transparent cages on a rack equipped with 30 small infrared cameras (CMTH with 1/4 inch Sony CCD, 3.6 mm lens), attached to a metal structure and placed at about 12 cm distance from the cage wall, allowing whole floor area detection (1 camera per each cage). Two infrared LEDs pointed towards the ceiling to provide diffuse infrared lighting in the room allowing for analysis of behavior. The cameras recorded 24 h/24 h and the video signals were acquired on two 16 channels DVR encoding H.264 format (Avtech,AVC798ZA). The Video Viewer Application1 (version 0.1.8.4) drove the video recording and replay. The active maternal behavior was analyzed from day 1 to day 5 after the birth of the offspring. Within each observation period, the behavior of each dam was scored every min (30 observations/h with 2h of observation per 5 days) for the following behaviors: licking, grooming, carrying pups (Champagne et al., 2003) and nursing behavior (active arched back nursing, blanket posture in which the dam lays over the pups, or passive posture in which the dam is lying either on her back or side while nursing the pups). Data obtained represent the active presence of the dam on the nest expressed in a percentage of the total number of observations.

4. Behavioral studies

4.1 Risk-taking behavior in an elevated-plus maze test

Risk-taking behavior of PRS or control adult and aged offspring (Marrocco et al., 2020) was assessed in the elevated-plus maze test (EPM; Pellow et al., 1985)). Briefly, the test was performed for 5 min in the afternoon, between 1 and 4 pm, and started by placing the rat with the head facing the closed arm in the center of the maze. We used two different EPM-apparatus for measuring the risk-taking behavior in adult and aged rats. Particularly, we used a standard EPM apparatus with closed and open arms measuring 10 × 10 cm for adults and a custom-made EPM apparatus (Vallée et al., 1999) with closed and open arms measuring 20 × 20 cm for aged rats. The luminosity was approximately 25 lx for the closed arm, and 50 lx for the open arm. Behavior was recorded by a video camera and manually scored by a trained observer blind to the animals' condition (PRS and control) using a specific software package (Noldus, The Observer®). The time spent in the open and closed arms and the latency to enter in the open arm were measured. The percentage of time spent in the open arms and the percentage of the latency to enter in the open arm were calculated and analyzed as risk-taking behavior.

4.2 Spatial recognition memory in Y-maze

Spatial recognition memory was measured in a two-trial memory task in a Y-maze (Vallée et al., 1999). The Y-maze is made of gray plastic with three identical arms (50 cm) enclosed with 32 cm high side walls. The maze was equipped with two infrared beams located at the end of each arm and the floor was covered with rat odor-saturated sawdust, which was mixed between each session to eliminate olfactory cues. Visual cues were placed in the testing

room and kept constant during the whole behavioral testing sessions. The luminosity was approximately 40lx. The test consists of two trials lasting 5 minutes separated by a time interval. In the first trail (acquisition phase), the animals were allowed to visit only two out of three arms of the Y-maze, since one of these was closed. During the intertrial interval the animals were housed in their home cages in a different room from the one of the test. In the second trial (retention phase), animals had free access to all the arms. The time spent in the novel arm (previously closed in the first trial) was measured and calculated as a percentage of the total time spent in all three arms during the first 3 min of the second trial. This time corresponds to the maximal exploratory activity in the novel arm, which subsequently declines (Dellu et al., 1992). Time spent in the novel arm above chance (i.e., 33%) indicates spatial recognition. Memory performance was tested with an intertrial interval of 6 h.

5. Isolation of synaptosomes

Synaptosomes, which have a diameter of 1µm , originate from nerve terminals (Breukel et al., 1997) from whose they retain the functional and the structural features, confirming their presynaptic origin. Cortical purified synaptosomes were prepared by homogenizing fresh cortical tissue with a glass/Teflon tissue grinder (clearance 0.25 mm) in 10 volumes of 0.32 M sucrose, buffered to pH 7.4 with Tris-(hydroxymethyl)-amino methane (TRIS, final concentration 0.01 M). Then, the homogenate obtained was centrifuged at 4°C at 1000 x g for 6 min to remove nuclei and debris. The resulting supernatant was gently stratified on a discontinuous Percoll® gradient (6%, 10% and 20% v/v in Tris-buffered sucrose) and then centrifuged at 33,500 x g for 5 min. The synaptosomal fraction, which is the layer between 10% and 20% of the Percoll® gradient was subsequently collected and washed to removing the Percoll ® by centrifugation with a physiological solution having the following composition:

NaCl, 140 mM; KCl, 3 mM; $MgSO_4$, 1.2 mM; $CaCl_2$, 1.2 mM; NaH_2PO_4, 1.2 mM; $NaHCO_3$, 5 mM; HEPES, 10 mM; glucose, 10 mM; pH 7.2-7.4). When indicated, the fresh cortex was homogenized in buffered sucrose containing 20 μM of pep2-SVKI or pep2-SVKE (purchased by Tocris Bioscience) in order to entrap these peptides into subsequently isolated synaptosomes (see Raiteri et al., 2000; Pittaluga et al., 2006)

6. Release study

Cortical synaptosomes were incubated in a rotary water bath maintained at 37°C for 30 min in the absence (control) or presence of the following antibodies recognizing the amino-terminus of the GluA proteins (final concentration 1:500): rabbit polyclonal anti-GluA1; rabbit monoclonal anti-GluA2; mouse monoclonal anti-GluA3; rabbit monoclonal anti-GluA4 in the chapter one; with patients' CSF titrated for anti-GluA3 autoantibodies in chapter two. At t = 15 min of incubation, the radioactive tracer [2,3-^{3}H]D-aspartate ([^{3}H]D-Asp, f.c.: 50 nM, (specific activity 11.3 Ci/mmol), Perkin Elmer) was added to label the synaptosomes (t = 30 min). The synaptosomal suspensions were equally layered on microporous filters at the bottom of a set of parallel chambers maintained at 37°C in a Superfusion System (Ugo Basile, Comerio, Varese, Italy; Raiteri et al., 1974; Pittaluga, 2016). Superfusion was started at a flow rate of 0.5 ml/min with the above reported standard physiological solution for 36 min to equilibrate the system. At t = 36 min, samples were collected according to the following scheme: fractions b1, from 36 to 39 min; b2, from 39 to 42 min; b3 from 43 to 45min and b4 from 45 to 48.

When indicated, at t= 39 min of superfusion, synaptosomes were exposed to (S)AMPA (Tocris Bioscience) in the presence of 10 μM cyclothiazide until the end of the release study (t =48 min). In the experiments dedicated to studying the impact of the complement and C1q-

depleted complement (Gentaur), the immune components were added to the standard physiological solution when the fraction b1 was collected and maintained for 90 sec being replaced with the physiological medium. When indicated, the AMPA receptor antagonist NBQX or the EAAT blocker DL-t-BOA (DL-threo-β-Benzyloxyaspartic acid) was added concomitantly to the agonist. NBQX and DL-t-BOA were purchased by by Tocris Bioscience (Bristol, UK).

Fractions collected and superfused synaptosomes were counted for radioactivity, which was expressed as a percentage of the total synaptosomal radioactivity. In each experimental condition, the [^{3}H]D-Asp release was calculated as the sum of the tritium (expressed as %) in the four fractions collected. The agonist-evoked overflow was calculated as the difference between the tritium released from synaptosomes exposed in superfusion to AMPA or to complement and synaptosomes superfused with the physiological medium.

7. Western blot analysis

Cortical purified synaptosomes prepared from three months old mice were lysed in modified RIPA buffer (10 mM Tris, pH 7.4, 150 mM NaCl, 1 mM EDTA, 0.1% SDS, 1% Triton X-100, 1mM sodium orthovanadate and protease inhibitors) and quantified for protein content with BCA assay. Samples were boiled for 5 minutes at 95°C in SDS-PAGE sample buffer. Proteins were separated by means of SDS–polyacrylamide gel electrophoresis; 10% precast polyacrylamide gel (Bio-Rad) were used. Proteins were then transferred to PVDF membrane. Membranes were saturated in Tris-buffered saline-Tween (t-TBS: 20 mM Tris, pH 7.4, 150 mM NaCl, and 0.05% Tween 20) containing 5% (w/v) non-fat dried milk for 1 h at 25°C, and then incubated overnight at 4°C with the following primary antibodies: rabbit anti-GluA1 (1:1000, # ab86141, abcam) and rabbit anti-GluA2 (1:2000, # ab206293, abcam),

mouse anti-GluA3 (1:500, #MAB5416, millipore), rabbit anti-GluA4 (1:500; # GTX62957, Genetex), rabbit polyclonal anti-synapsin Ia/b (1:4000; #20780), rabbit polyclonal anti-synaptophysin (1:8000; #9116), rabbit polyclonal anti-syntaxin (1:4000, #13994), rabbit polyclonal anti-synapsin IIa (1:4000; #25538), all purchased from Santa Cruz Biotechnology; mouse monoclonal anti-rab3a (1:2000, #107111), mouse monoclonal anti-Munc-18 (1:2000; #116011), mouse polyclonal anti-VAMP (1:1500; #104 111), which were purchased from Synaptic Systems; After 3 x 5-min washes in tween-TBS, membranes were incubated with the appropriate horseradish peroxidase-linked secondary antibodies (purchased by Sigma) for 1 hour at room temperature. After 3 x 10-min washes in tween-TBS the protein bands were detected and analyzed for optical density using an enhanced chemiluminescence substrate (ECL, LiteAblot PLUS, Euroclone, Milan, Italy) and a chemiluminescence system (Alliance 6.7 WL 20M, UVITEC, Cambridge, UK), and UV1D software (UVITEC).

8. Confocal microscopy

Purified synaptosomes (40µg of total protein) obtained from the cortex of adult male C57BL/6J mice were fixed with 2% paraformaldehyde (15 min), washed with phosphate-buffered saline (PBS) and then permeabilized with 0.05% Triton X-100. After washing with PBS containing 0,5% BSA (bovin serum albumin), the synaptosomes were incubated overnight at 4°C with the following primary antibodies diluted in PBS containing 3% BSA: rabbit polyclonal anti-GluA1 (1:1000), rabbit monoclonal anti-GluA2 (1:200), mouse monoclonal anti-GluA3 (1:500), rabbit monoclonal anti-GluA4 (1:500), goat polyclonal anti-syntaxin 1A (1:4000, Chemicon) and guinea pig anti-vesicular glutamate transporter type 1 (VGLUT1; 1:1000, Millipore). After washing in PSA, synaptosomes were then incubated for 1 hour at 25°C with the respective secondary antibodies purchased from Life Technologies Corporation:

donkey anti-goat AlexaFluor-488, goat anti-guinea pig AlexaFluor-488 and donkey anti-rabbit AlexaFluor-647, (1:1000, colocalization of GluA1/ GluA2/ GluA4 receptor proteins with syntaxin 1A or VGLUT1), and, donkey anti-goat AlexaFluor-488, goat anti-guinea pig AlexaFluor-488 and donkey anti-mouse AlexaFluor-647 (1:1000, colocalization of GluA3 receptor proteins and syntaxin 1A or VGLUT1). Synaptosomes were then applied onto coverslips.(Olivero et al., 2019). Fluorescence imaging (512 x 512 x 8 bit) acquisition was performed by a six-channel Leica TCS SP5 laser-scanning confocal microscope, equipped with 458, 476, 488, 514, 543 and 633 nm excitation lines, through a plan-apochromatic oil immersion objective 63X/1.4NA. Light collection configuration was optimized according to the combination of chosen fluorochromes and sequential channel acquisition was performed to avoid spectral bleed-through artifacts. Leica 'LAS AF' software package was used for image acquisition, storage and visualization. The quantitative estimation of co-localized proteins was performed by calculating the 'co-localization coefficients'(Manders et al., 1993; WCIF Colocalization Plugins, Wright Cell Imaging Facility, Toronto Western Research Institute, Canada) in the Image J 1.51w software.

9. Biotinylation studies

The amount of GluA2 and GluA3 subunits protein in cortical synaptosomal plasma membrane were evaluated by biotinylation and subsequent immunoblot analyses (Olivero et al., 2018). Briefly, purified mouse cortical synaptosomes were divided into 4 aliquots: the first one was lysed in modified RIPA buffer to analyse the GluA subunit content in the total synaptosomal lysate (L), while the remaining three aliquots were incubated for 30 minutes at 37° C in a rotary water bath in the absence (control synaptosomes, C) or presence of rabbit anti-GluA2 antibody (1:500, anti-GluA2 incubated synaptosomes) and of mouse anti-GluA3

antibody (1:500, anti-GluA3 incubated synaptosomes). The control (C) and the anti-GluA incubated synaptosomes were then treated with sulfo-NHS-SS-biotin (1.5 mg/ml) in a PBS/ca-Mg medium with the following composition (mM): 138 NaCl, 2.7 KCl, 1.8 KH_2PO_4, 10 Na_2HPO_4, 1.5 $MgCl_2$, 0.2 $CaCl_2$, pH 7.4 for 1 h at 4°C. The samples were then incubated with PBS/Ca-Mg containing 100 mM glycine for 20 min at 4°C to quench the reaction. After two washes, biotinylated synaptosomes were lysed in modified RIPA buffer and identical amount of samples (100 µg) incubated with Dynabeads MyOne Streptavidin T1 beads for 30 min at 25°C under shaking to pull-down the biotinylated proteins. Dynabeads were also added to the non-biotinylated synaptosomes to verify the specificity of streptavidin pull-down (B). After extensive washes, all the samples were boiled for 5 min at 95°C in SDS-PAGE loading buffer to separate biotinylated proteins from the beads. Eluted fractions were analyzed through immunoblot assay (see Western blot analysis section). The immunoreactivity of GluA2 and GluA3 receptor proteins was monitored in the total lysate (L), in control (C), in anti-GluA2 or anti-GluA3 incubated biotinylated synaptosomes (anti-GluA2 and anti-GluA3 incubated synaptosomes) as well as in the streptavidin pull-down of the non-biotinylated synaptosomal lysate (B) by using rabbit anti-GluA2 (1:2000) and mouse anti-GluA3 (1:500) antibodies.

10. Measurement of interleukin-6 levels

Il-6 (pg/mL) were determined in the plasma extracted from blood samples. Plasma was collected by using ethylenediaminetetraacetic acid (EDTA) as an anticoagulant and centrifuged (15 min at 1000 × g) at 4 °C. Plasma was stored at -20 °C until assessment. The enzyme-linked immunosorbent assay (ELISA) kits (CUSABIO (CSB-E04640r); sensibility range 0.312 pg/ml-20 pg/ml) were used according to the manufacturer's protocol. All standards, blood samples, and controls were analyzed concurrently in duplicate. The optical density of the

samples was determined at 450 nm using a microplate reader (BioTek Instruments, Winooski, USA).

11. Partial correlation

The correlation between IL-6 plasma levels (pg/mL) and the risk-taking behavior was calculated after controlling for sex and group (PRS/CONT) on both measures to determine significant relationships between the two. Moreover, $\beta 1 \neq 0$ indicates a significant correlation between X and Y.

12. Statistics and calculations

Sigma plot 10 data analysis software package was used for data handling / statistics. Analysis of variance was performed by ANOVA (with group and sex as independent variables) and followed by Dunnett's multiple-comparisons test or Fisher test, as appropriate; direct comparisons were performed by Student's *t*-test. The level of significance was set at $p< 0.05$.

RESULT AND DISCUSSION

Chapter 1.

AMPA autoreceptors and their relevance to autoimmune diseases

(Cisani et al., 2021)

In recent years antibodies emerged as useful tools to characterize by a pharmacological point of view both ionotropic and metabotropic receptors also permitting to decipher their subunits composition.

As already introduced, AMPA receptors consist of associations of dimers but the lack of selective ligands for each GluA subunit makes almost impossible the prediction of the subunit composition. In the CNS, the AMPA receptors localize at the synaptic level, having either a presynaptic and a postsynaptic localization (Cheramy et al., 1991; Pittaluga et al., 1997; Collingridge et al., 2004; Summa et al., 2011). As far as the presynaptic release-regulating AMPA-receptors are concerned, evidences in the literature demonstrate the existence of presynaptic AMPA heteroreceptors controlling the release of acetylcholine, dopamine, noradrenaline, GABA (Pittaluga et al., 1997) and of AMPA autoreceptors (Summa et al., 2011) having so far an unknown subunit composition. In an attempt to bypass the limitation due to the lack of selective ligands, I approached the pharmacological characterization of the presynaptic release-regulating AMPA receptors in cortical isolated nerve endings (i.e. the synaptosomes) with the “immuno-pharmacological approach”, which consists in using

antibodies recognizing the amino-terminal of the receptor subunits to evaluate their impact on the receptor-mediated functions. In particular, by binding the targeted protein sequences, the antibodies modify the distribution of the subunit structure either mimicking orthosteric and allosteric agonists or behaving as selective antagonist, indirectly modulating their ability to control the transmitter exocytosis.

This approach was already used to hypothesize the subunit composition of either metabotropic and ionotropic receptors and in most cases the prediction was soon after confirmed by using selective subunit-specific ligands. It is the case of the antibodies recognizing the amino-terminal of mGlu2 and mGlu3 subunits, which allowed the prediction of the composition in mGlu subunits of the II° group of mGlu autoreceptors controlling glutamate exocytosis in cortical and spinal cord synaptosomes (Olivero et al., 2017) that was soon after confirmed by using orthosteric and allosteric tools (Olivero et al., 2017).

Similarly, the pharmacological profile of the CCRs involved in the CCL5-mediated control of glutamate in human and rat cortical synaptosomes was predicted by using antibodies recognizing the amino-terminus of the CCR subtypes (namely the CCR1, CCR3 and 5) and confirmed with the specific chemical ligands (Di Prisco et al., 2012).

Finally, it was confirmed the participation of GluN1, GluN2A, GluN2B and GluN3B subunits to the expression of NMDA autoreceptors in hippocampal nerve endings by using either anti-GluN antibodies recognizing the amino-terminal of receptor proteins or selective GluN ligands (Olivero et al., 2019).

Based on the promising results, I decided to apply the “immuno-pharmacological approach” also to characterize the subunit composition of the AMPA autoreceptors in cortical synaptosomes. Antibodies recognizing the amino-terminus of the GluA1 to 4 subunit proteins were screened based on their ability to highlight the presence of the receptor protein with biochemical approaches as well as to interfere with the AMPA-evoked releasing activity.

Over the past 20 years, several CNS disorders affecting the hippocampal and the cortical functions have been shown to associate with the production of autoantibodies recognizing synaptic proteins, ion channels, or neuronal receptors such as NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, $GABA_A$ receptors, and dopamine D2 receptors. In general, it is proposed that autoantibodies can cause changes in the insertion, localization, and function of the respective antigens (i.e. the receptors themselves). Particularly, antibodies recognizing the NMDA receptor subunits (for instance, the GluN1 and the GluN2A and B subunits, Monyer et al., 1992; Paoletti et al., 2013; Banerjee et al., 2016) as well as the serum of patients with anti-GluN antibodies accelerate the internalization of the NMDA receptors in neurons, impairing their signaling at chemical synapses (Moscato et al., 2014; Dalmau, 2016).

The functional adaptations induced by autoantibodies are also detectable in isolated nerve endings. Indeed, in recent years it was shown that antibodies recognizing the extracellular sequence of the GluN subunit proteins antagonize the NMDA-mediated releasing activity at glutamatergic nerve endings, by accelerating the internalization of the NMDA receptors, then interfering with the excitatory signaling at chemical synapsis in CNS. Different from the anti-GluN, the impact of autoantibodies recognizing the subunits involved in the expression of the AMPA receptors (the GluA1 to 4 subunits) in the synaptic plasticity still represents a matter of debate. Contrasting results emerged when studying the respective impact on synaptic transmission of autoantibodies from patients suffering from anti-AMPA encephalitis and commercially available AMPA receptor antibodies (Peng et al., 2015; this aspect will be deeply discussed in the chapter 2 of results). Furthermore, several shreds of evidence suggest that the complement could have a role in the anti-GluA sera containing effects, but the link between the autoantibodies and the complement complex is far to be elucidated (Paas, 1998; Whitney and McNamara, 2000).

To improve the knowledge of the mechanisms involved in anti-AMPA autoimmune diseases, I also extended the study to verify the impact of the presence of the anti-GluA-GluA subunit antigen-antibody complex at the outer side of the synaptosomal membranes on the complement-mediated releasing activity from nerve endings.

1.1 Characterization of AMPA presynaptic release-regulating autoreceptors in cortical nerve endings

1.1.1 On the existence of GluA subunits in cortical glutamatergic synaptosomes

In order to evaluate the presence of the four GluA subunits in the cortical nerve endings of adult mice, I first performed the western blot analysis with selective antibodies recognizing the amino-terminal sequence of the GluA subunits.

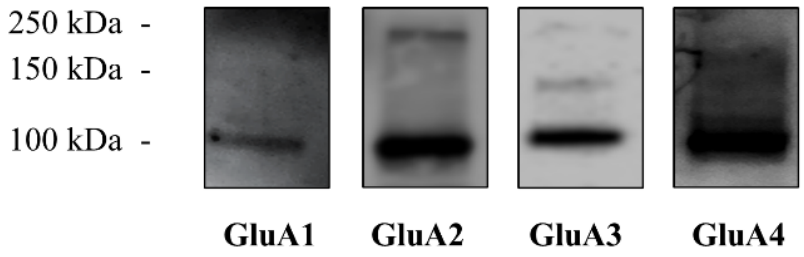


Figure 1. Mice cortical synaptosomes possesses GluA1 to 4 receptor subunits. The expression of GluA1, GluA2, GluA3 and GluA4 subunits of AMPA receptor was investigated in mouse cortical synaptosomes. The figure shows representative blots of three analyses carried out on different days.

The analysis of the cortical synaptosomal lysates unveiled a marked GluA1 to GluA4 positivities (Figure 1) having a mass consistent with the monomeric form of the respective receptor subunits (~110 kDa), well in line with data in the literature (Feligioni et al., 2006; Summa et al., 2011; Haglerød et al., 2017).

Confocal analysis was then performed to confirm the presence of the AMPA receptor subunits in cortical synaptosomes using as a marker of the nerve terminals the Syntaxin-1A (Stx-1A) protein. Figure 2 unveiled that the GluA 1, 3, and 4 subunits are expressed in cortical Stx-1A-immunopositive particles almost to a comparable level, amounting respectively to 44 ± 5 %, 46 ± 9 %, and 41 ± 11 % of the total of synaptic terminals positive for the anti- Stx-1A antibody. Differently, the GluA2 subunit was expressed to a low level (27 ± 5 %). In an attempt to focusing on glutamatergic terminals, the cortical synaptosomes were then labeled with the vesicular glutamate transporter type 1 (VGLUT-1) used as a selective marker of the glutamatergic particles. The quantification of the proteins colocalization revealed that: 91± 3% of VGLUT-1 positive synaptosomes express GluA1-immunoreactivity (Figure 3, panel “c”); 83±3% of VGLUT-1 positive synaptosomes express GluA2-immunoreactivity (Figure 3, panel “f”); 92±4% of VGLUT-1 positive synaptosomes express GluA3-immunoreactivity (Figure 3, panel “i”) and 77±4% VGLUT-1 positive synaptosomes express GluA4-immunoreactivity (Figure 3, panel “n”). The percentage of the total amount of glutamatergic synaptosomes is 60%. These results strongly support the presence of GluA receptor subunits in the glutamatergic terminals.

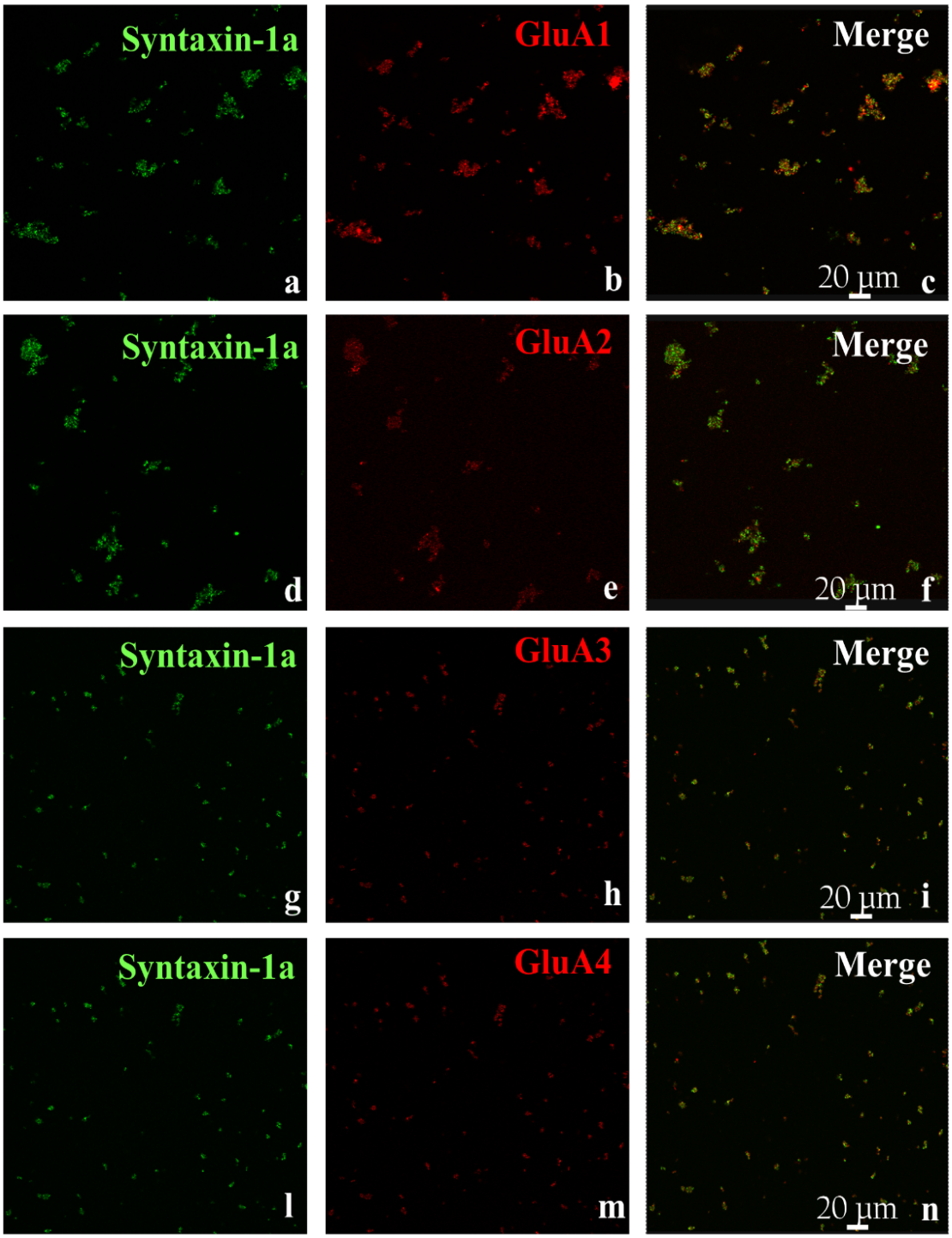


Figure 2. The colocalization of GluA subunits with Syntaxin-1A in adult mice cortical synaptosomes. Confocal microscopy unveiled a significant colocalization of GluA1 (red, b), GluA2 (red,e), GluA3 (red,h) and GluA4 (red,m) subunit and Syntaxin-1a (green, a, d, g and l, respectively) immunopositivies (merge, yellow, c, f, i and n, respectively). The figure shows representative images of three independent experiments from different animals.

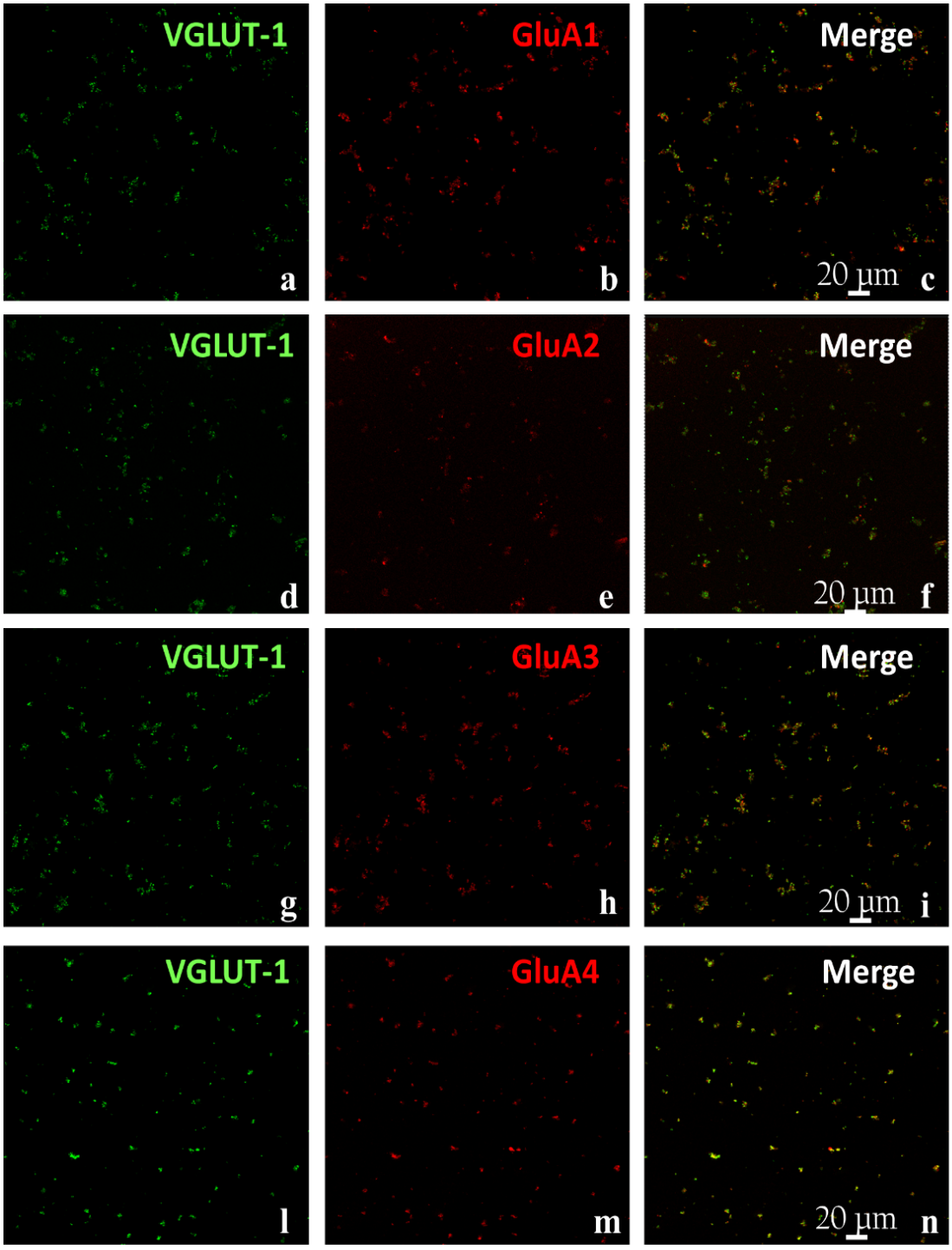


Figure 3. The colocalization of GluA subunits with Vesicular Glutamate Transporter type 1 in adult mice cortical synaptosomes. Confocal microscopy unveiled a significant colocalization of GluA1 (red, b), GluA2 (red,e), GluA3 (red,h) and GluA4 (red,m) subunit and VGLUT1 (green, a, d, g and l, respectively) immunopositivies (merge, yellow, c, f, i and n, respectively). The figure shows representative images of three independent experiments from different animals.

1.1.2 On the existence of release-regulating presynaptic AMPA autoreceptors in mice cortical synaptosomes

To verify the existence of the presynaptic AMPA autoreceptors in mouse cortical nerve terminals, experiments were carried out to demonstrate whether the release of glutamate from cortical synaptosomes is modified by exposing them to AMPA. The experimental approach used to this aim was "the up-down superfusion of a thin layer of synaptosomes", which is considered an experimental technique particularly suitable to study the modulation of neurotransmitters release mediated by presynaptic receptors. This technique was set up by Maurizio Raiteri and colleagues (Raiteri et al., 1974) and implemented in our lab during years to characterize by a functional point of view the subunit composition and the role of presynaptic release-regulating receptors. Briefly, synaptosomes are stratified as a thin monolayer on a microporous filter and are continuously up-down superfused with the physiological medium. Then, the superfusate fractions are collected to monitor the release of neurotransmitters. The release of neurotransmitters from synaptosomes can be evoked by adding selective receptor ligands in the superfusion medium. Under these experimental conditions the ligand induces changes to the neurotransmitter release that can only be attributed to its interaction with the respective receptor, since the continuous up-down superfusion removes any endogenous substance that would interfere with the signals (Raiteri and Raiteri, 2000; Pittaluga, 2017, 2019). The exposure of mice cortical synaptosomes preloaded with [^{3}H]D-Aspartate ([^{3}H]D-Asp; an analogous of glutamate non-metabolizable) to (S)AMPA (50 μM) caused a significant increase in the release of tritium (Figure 4), which was abolished by the concomitant presence of the AMPA antagonist NBQX (Figure 4). This result confirmed that the activation of presynaptic release-regulating AMPA autoreceptors accounted for the releasing effect observed in the experiments (see also Pittaluga et al., 1997).

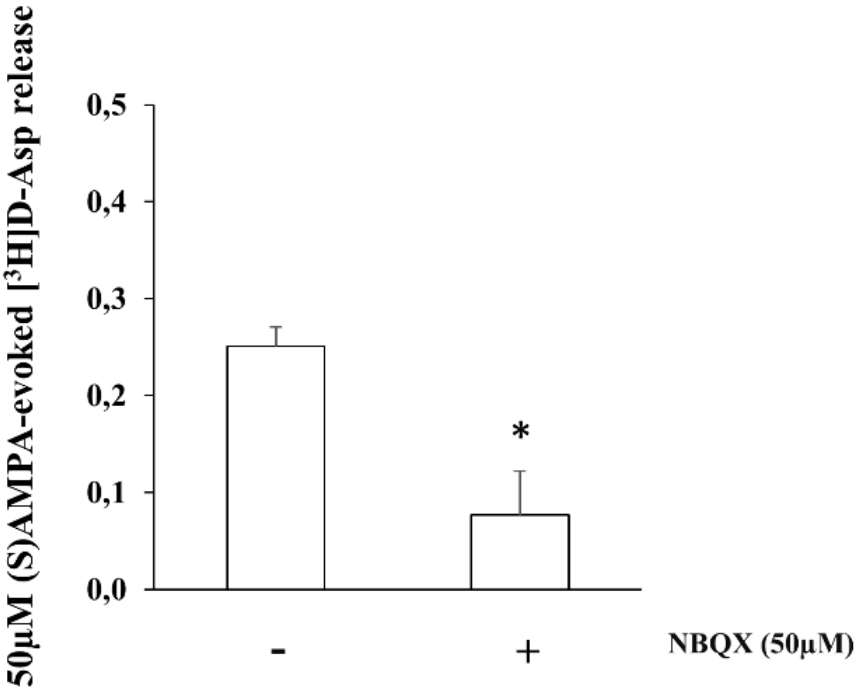


Figure 4. Effects of the AMPA receptor antagonist NBQX on the (S)AMPA-evoked release of [^{3}H]D-Asp from mice cortical synaptosomes. Mice cortical synaptosomes were labelled with the radioactive tracer([^{3}H]D-Asp) and exposed in superfusion to 50 µM (S)AMPA in the presence of 10 µM cyclothiazide to monitor tritium exocytosis. NBQX (50 µM) was added concomitantly to the agonist. Results are expressed as agonist-evoked tritium overflow. The (S)AMPA-evoked overflow was calculated as release above the spontaneous release. Values are expressed as means ± S.E.M. of data from three experiments run in triplicate. * = $p < 0.05$ versus 50 µM (S)AMPA.

1.1.3 Immuno-pharmacological characterization of the presynaptic release-regulating AMPA autoreceptors in cortical synaptosomes

As already introduced, I applied the "immuno-pharmacological approach" (Olivero et al., 2017 and 2019b), which relies on the use of selective commercially available anti-GluA antibodies as selective ligands, to characterize the subunit composition of the receptors under study (Gupta et al., 2008). Taking in consideration that the binding of selective antibodies to the respective receptor(s) at the extracellular site can cause the activation or the blockage of the receptor activity.

In order to evaluate whether and to what extent the antibodies interfere with the AMPA-evoked releasing activity, synaptosomes were incubated in the absence (control) or in the presence of the anti-GluA antibodies (1:500) used in confocal microscopy and western blot analyses, end soon after labelled with the radioactive tracer. The first result obtained was that the anti-GluA1 to anti-GluA4 antibodies did not modify on their own the basal release of [^{3}H]D-Asp from cortical synaptosomes [Control synaptosomes: 0,66±0,07; anti-GluA1 incubated synaptosomes: 0,69±0,1; anti-GluA2 incubated synaptosomes: 0,58±0,02; anti-GluA3 incubated synaptosomes: 0,71±0,06; anti-GluA4 incubated synaptosomes: 0,71±0,07; results represent the release of preloaded [^{3}H]D-aspartate in the first fraction collected (the basal release) of four experiments and they are expressed as percentage of the total [^{3}H]D-aspartate synaptosomal content]. These results suggest that the antibodies do not exert on their own any releasing activity and therefore that they do not mimic the pure agonist AMPA. Differently, when synaptosomes incubated with the anti-GluA antibodies were exposed in superfusion to (S)AMPA (50 μM) I observed significant changes to the AMPA-evoked releasing activity that strictly depended on the pre-incubation with antibody. For instance, I found a significant increase in the release of tritium from synaptosomes incubated with anti-

GluA2 or anti-GluA3 antibodies compared to control. Conversely, the incubation of cortical synaptosomes with anti-GluA1 or anti-GluA4 was ineffective on the release. (Figure 5A). Moreover, when NBQX (50 μM) was added concomitantly to the agonist, the release of glutamate evoked by (S)AMPA from anti-GluA2 or anti-GluA3-incubated synaptosomes was largely prevented (Figure 5B), which confirmed that the AMPA receptors accounted for the facilitation of the releasing activity but it also excluded the possibility that the facilitation of the AMPA-evoked releasing activity relied on non-specific events. Thus, the use of selective anti-GluA2 and anti-GluA3 antibodies caused functional changes in the AMPA-evoked releasing activity allowing the conclusion that cortical AMPA autoreceptors preferentially consist of GluA2 and GluA3 subunits.

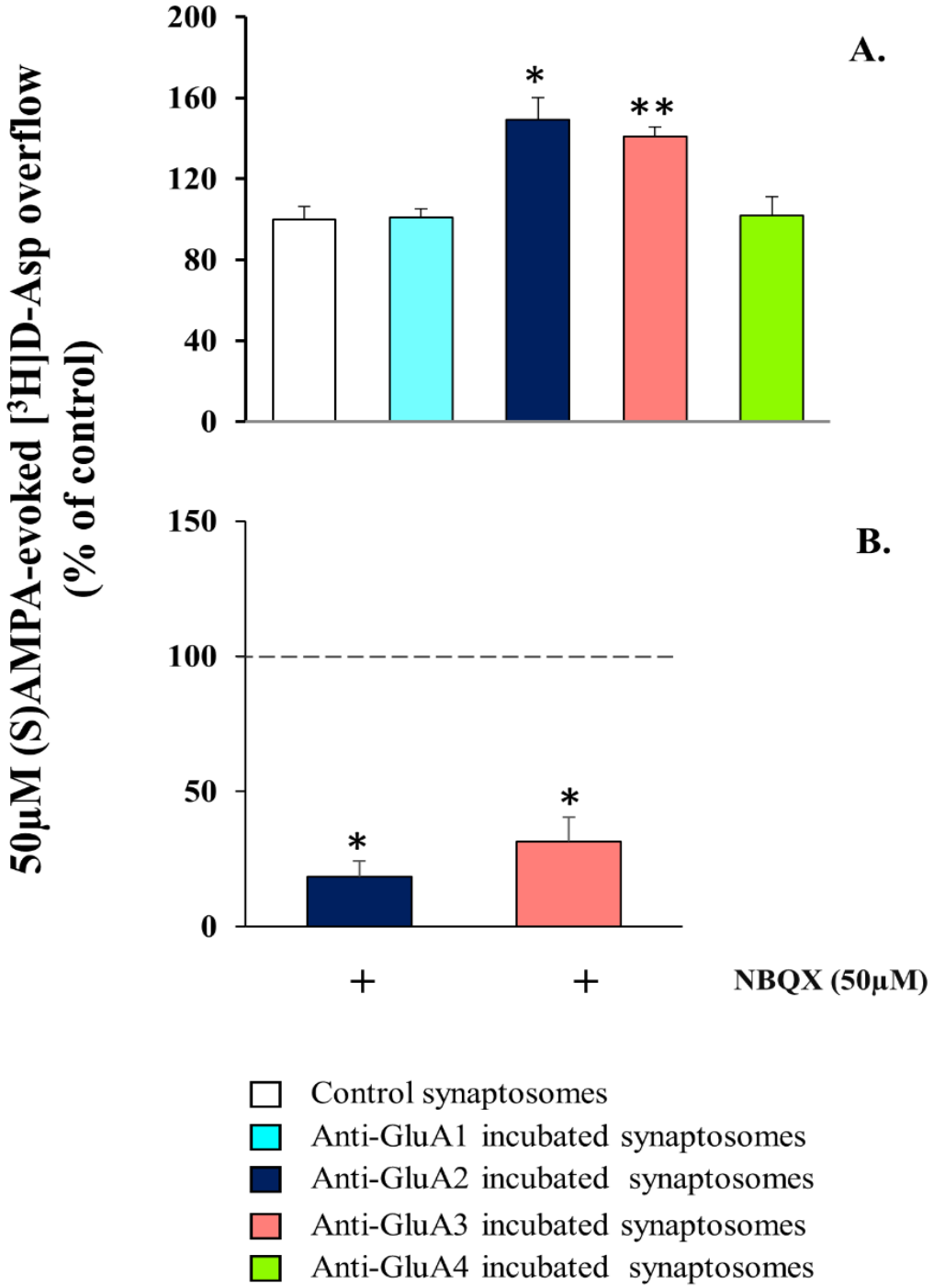


Figure 5. Effects of the incubation of cortical synaptosomes with anti-GluA antibodies on the (S)AMPA-evoked release of [^{3}H]D-Asp: antagonism by NBQX. Mice cortical synaptosomes were incubated in the absence (control) or in the presence of selected anti-GluA antibodies (as indicated) and then preloaded with tritium and exposed in superfusion to (S)AMPA (50 µM)/ cyclothiazide (10 µM) alone (A) and in presence of NBQX (50 µM, B) to monitor the exocytosis of [^{3}H]D-Asp. Results are expressed as percentage of the (S)AMPA-evoked release from control synaptosomes (% of control). The (S)AMPA-evoked overflow (expressed as % of tritium over basal release) amounted to 0.32 ± 0.02. Data are reported as means ± S.E.M. from three experiments run in triplicate. * = $p < 0.05$ versus respective control; ** = $p < 0.01$ versus respective control.

1.1.4 Anti-GluA2 and anti-GluA3 antibodies increase the surface density of presynaptic release-regulating AMPA autoreceptors in cortical synaptosomes

Based on the finding that evident changes of the AMPA-evoked releasing activity were only observed in synaptosomes incubated with anti-GluA2 and anti-GluA3 antibodies, I asked whether the incubation of the synaptosomes with the antibodies could have affected the surface density of the AMPA receptors themselves, as already observed for NMDA (Olivero et al., 2019). Biotinylation studies were carried out to answer the question and the data are described in Figure 6. The density of the biotin-tagged GluA2 subunits was significantly increased in both anti-GluA2 (Figure 6a and b), and anti-GluA3 incubated synaptosomes (Figure 6 a and c) compared to control (C). Similarly, pre-incubation of mouse cortical synaptosomes with anti-GluA2 and anti-GluA3 antibodies increases the immune reactivity of the GluA3 subunit. Although both antibodies increased the surface expression of the two subunits, the density of the GluA3 subunit was significantly increased in both anti-GluA incubated particles. In a whole the results could suggest that the presence of antibodies recognizing the NH_2 terminal of the GluA2 and GluA3 subunits causes an unbalance in the GluA2:GluA3 ratio in the AMPA receptors, making the GluA3 component prevailing on the GluA2 one. Notably, this unbalance would dramatically affect the Ca^{2+} sensitivity of the associated channel as already discussed in the section 1.2 of the Introduction and this would largely impact the releasing activity of the receptor itself. Actually, when involved in the receptor assembly, the GluA3 subunit favors the calcium ions influx, whereas the GluA2 subunit makes the receptor mainly calcium impermeable as a result of GluA2 mRNA editing (Sommer et al., 1991). Thus, the increased GluA3 subunit expression in the incubated synaptosomes would be expected to increase the calcium dependency of the receptors, which would results in an amplified exocytosis of glutamate as indeed observed in the release experiments.

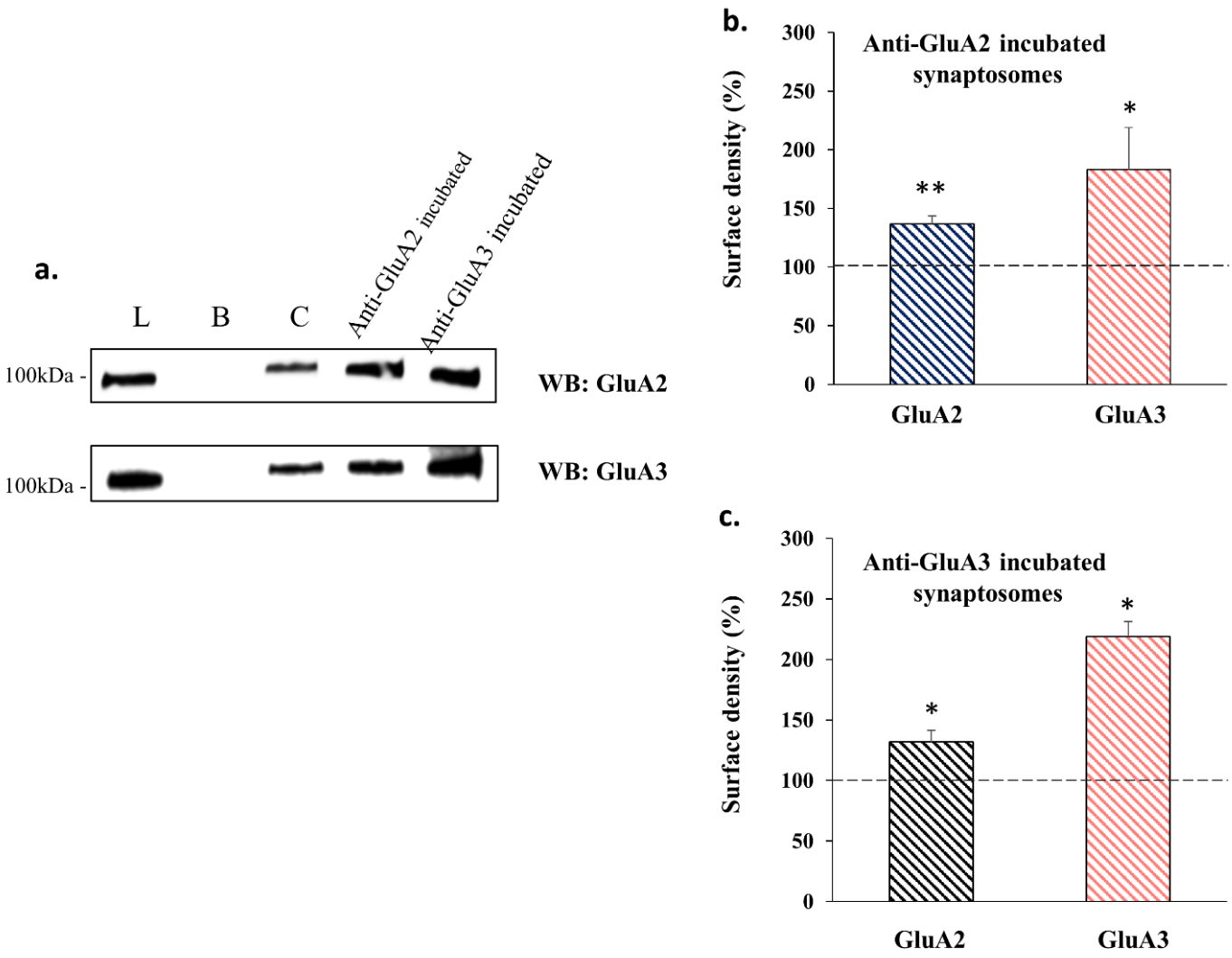


Figure 6. GluA2 and GluA3 subunits surface densities in cortical synaptosomes incubated with anti-GluA2 and anti-GluA3 antibodies. (a) The immunoblot of GluA2 and GluA3 compares total synaptosomal lysates (L), synaptosomal lysates not treated with biotin, but subjected to streptavidin pulldown (B), control synaptosomal lysates treated with biotin and subject to streptavidin pulldown (C), and anti-GluA2 and anti-GluA3 incubated synaptosomal lysates treated with biotin and subject to a streptavidin pulldown. The blot is representative of three different experiments carried out on different days on synaptosomal preparations obtained from different animals. b and c represent the changes of the surface density of GluA2 (blue left rising hatched bar) and GluA3 (coral pink left rising hatched) subunits in anti-GluA2 (b) or anti-GluA3(c) incubated cortical synaptosomes. Data are expressed as percentage of the respective control and are reported as means ± S.E.M. * = $p < 0.05$ versus respective control; ** = $p < 0.01$ versus respective control.

1.1.5 Presynaptic release-regulating AMPA receptors traffic in a constitutive manner in mouse cortical synaptosomes

The biotinylation study also suggested that the cortical presynaptic release-regulating AMPA receptors could traffic in and out the synaptosomal plasma membranes. As already introduced in the section 1.3 of the introduction, the AMPA receptors are dynamic entities continuously added and removed in and out of synaptic membranes in basal condition (constitutive trafficking) as well as in response to neuronal activity (regulated trafficking; Song and Huganir, 2002; Esteban, 2003; Malenka, 2003; Henley et al., 2011; Henley and Wilkinson, 2016). Particularly, the constitutive trafficking takes place also at the presynaptic level (Pittaluga et al., 2006; Summa et al., 2011; Haglerød et al., 2017), where it involves GluA2/GluA3-containing AMPA receptors (Esteban, 2003). The GluA2 and GluA3 carboxyl-domain directly interacts with the PDZ-domain of GRIP, ABP, and PICK1, which are involved in the constitutive trafficking and regulate the receptors surface expression. The interaction between these proteins and the carboxyl-domain of the GluA subunits can be disrupted by entrapping synaptosomes with pep2-SVKI, a peptide corresponding to the last ten amino acid sequence of the intracellular C-terminal domain of the GluA2 subunit. By binding the intracellular domain of the AMPA subunits, Pep2-SVKI causes the blockage of the receptor internalization, favoring its stabilization in the synaptosomal plasma membrane. The consequence of this event is the enhancement of the number of AMPA receptors expressed at the surface level, which in turn reinforces the AMPA receptor releasing activity.

Mouse cortical synaptosomes have been entrapped with Pep2-SVKI, the active peptide, and with Pep2-SVKE, the negative control peptide. I found that the release of glutamate evoked by AMPA was significantly increased when pep2-SVKI was introduced into cortical nerve endings compared to control synaptosomes, whereas pep2-SVKE was devoid of activity

(Figure 7). The effect observed could be discussed by assuming that pep2-SVKI triggers the increased AMPA-evoked releasing activity by stabilizing the receptor in the synaptosomal plasma membrane. Furthermore, it indicates that the presynaptic AMPA receptors would mainly consist of GluA2/GluA3 subunits, which traffick in a constitutive manner in mouse cortical synaptosomes. Both the entrapped pep2-SVKI and pep2-SVKE did not modify on their own the spontaneous release of glutamate.

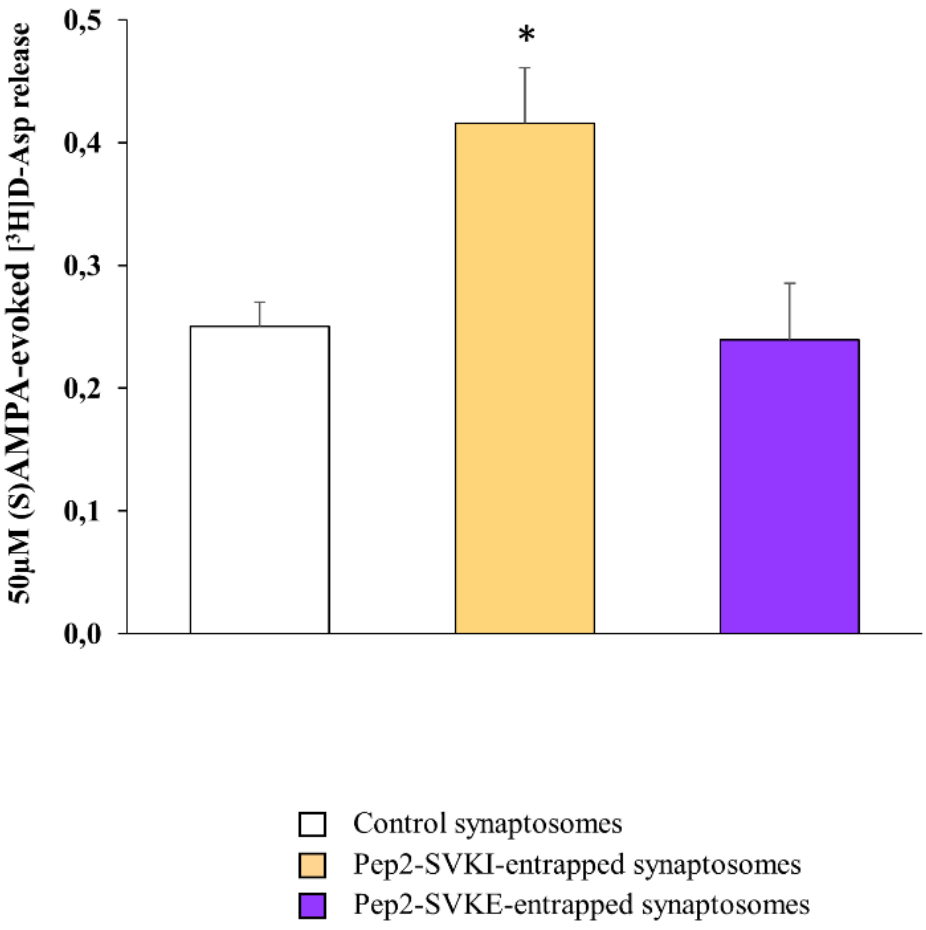


Figure 7. Effects of pep2-SVKI and pep2-SVKE on (S)AMPA-evoked tritium release from mice cortical synaptosomes. Cortical synaptosomes were exposed to (S)AMPA (50 μM) in presence of cyclothiazide (10 μM). pep2-SVKI and pep2-SVKE were entrapped into synaptosomes as reported in the Method section. Results are expressed as agonist-evoked tritium overflow and are reported as the means ± S.E.M. * = $p < 0.05$ versus control.

In conclusion these results proved that i) the subunit composition of cortical AMPA autoreceptors preferentially consists of GluA2 and GluA3 subunits; ii) the presence of anti-GluA2 and anti-GluA3 antibodies increases, although to a different extent, the surface density of the GluA2 and GluA3 subunits; iii) the cortical GluA2- and GluA3-containing AMPA autoreceptors trafficking in and out the plasma membrane in a constitutive manner.

1.2 Auto anti-GluA antibodies and immune responses: the role of complement

1.2.1 Anti-GluA2 and anti-GluA3 antibodies improves the complement-induced releasing activity

In recent years it was demonstrated that the complement releases glutamate from nerve terminals isolated from different CNS regions through a mechanism involving carrier-mediated processes (Merega et al., 2014). The authors also found that the classic pathway of complement activation can be triggered when synaptosomes bear an antibody-protein complex at the outer side of the plasma membranes (Merega et al., 2015). When activated, this pathway further increases the releasing activity of complement at glutamatergic nerve terminals. We asked whether the presence of the anti-GluA/GluA complex could affect the release of glutamate elicited by complement from mouse cortical synaptosomes. To this aim, control and anti-GluA1 to anti-GluA4 incubated synaptosomes were exposed to complement (1: 300 dilution), and then the release of tritium was monitored. I found that the complement-induced release of glutamate from cortical synaptosomes incubated with either the anti-GluA2 or anti-GluA3 antibody was significantly increased when compared to control (Figure 8). Differently, the

incubation of synaptosomes, respectively, with anti-GluA1 and anti-GluA4 did not cause any change in the complement-induced release of glutamate (Figure 8). The increased glutamate release from anti-GluA2 and anti-GluA3-incubated synaptosomes evoked by the complement was prevented by the concomitant addition of the excitatory amino acid transporter blocker DL-t-BOA (Figure 9A) while the presence of the AMPA antagonist NBQX did not cause any changes (Figure 9B). The efficacy of DL-t-BOA in reducing the releasing activity compared to the level of efficacy of NBQX suggested that the complement-induced release from cortical glutamatergic synaptosomes involves carrier-mediated processes and not AMPA receptor-mediated mechanism(s).

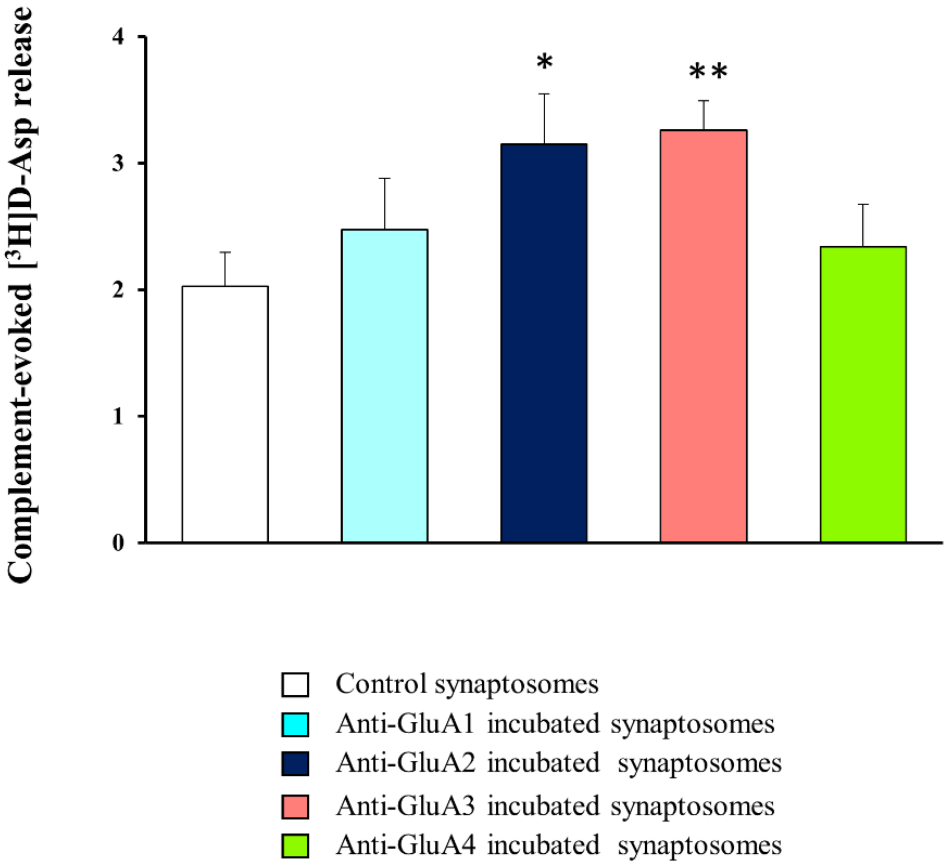


Figure 8. Effects of the incubation of mice cortical synaptosomes with anti-GluA subunit antibodies on the (1:300) complement-evoked release of [^{3}H]D-Asp. Mice cortical synaptosomes were incubated in the absence (control) or in the presence of selected anti-GluA antibodies (as indicated) and then preloaded with tritium and exposed in superfusion to the complement (dilution 1:300). Results are expressed as complement-evoked tritium overflow and are reported as the means ± S.E.M from five experiments run in triplicate. * = $p < 0.05$ versus control; ** = $p < 0.01$ versus control.

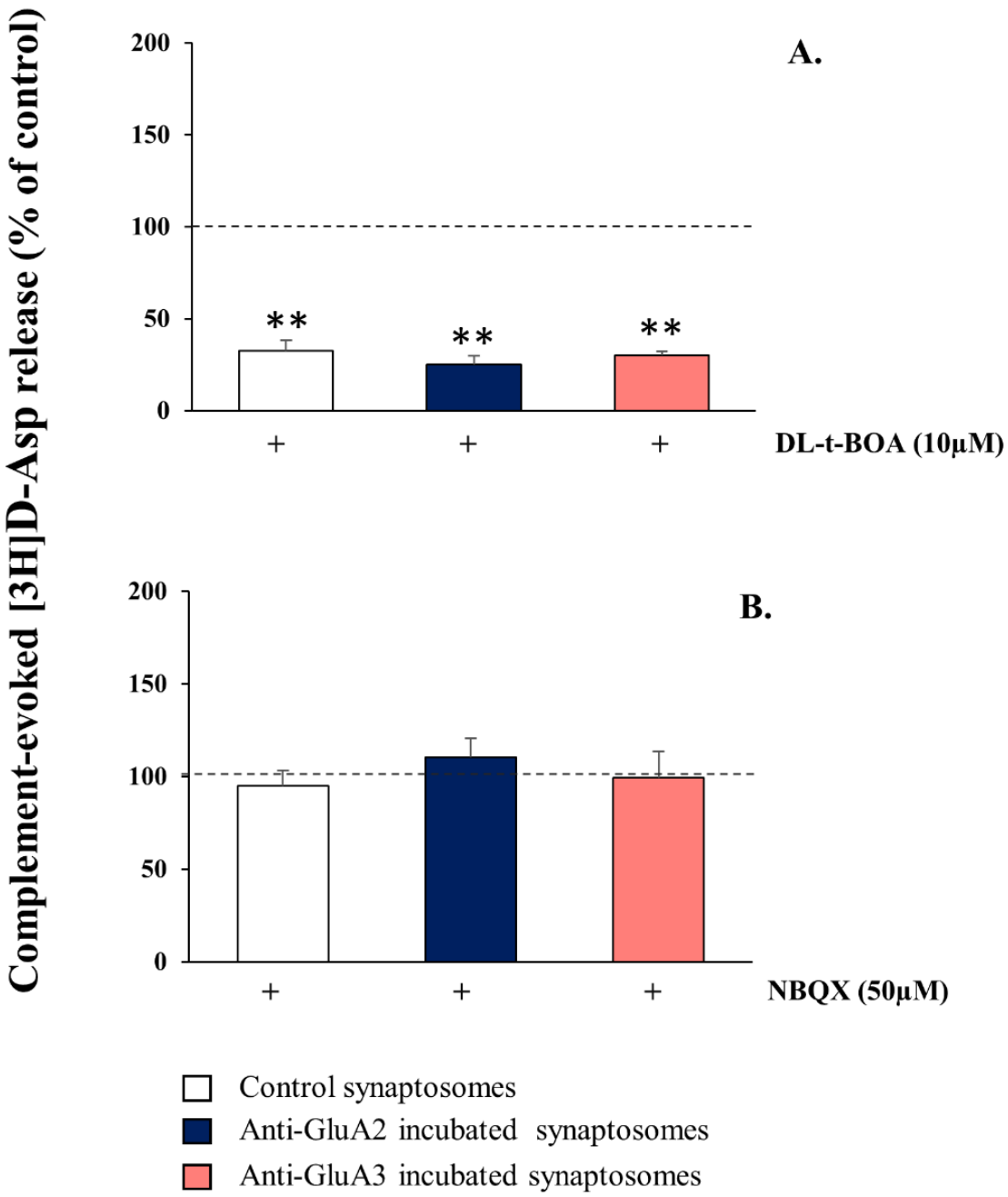


Figure 9: Effects of DL-t-BOA and NBQX on the complement-evoked release of tritium from mice cortical synaptosomes incubated with anti-GluA2 and anti-GluA3 subunit antibodies. Mice cortical synaptosomes were incubated in the absence (control) or in the presence of anti-GluA2 (dark blue bar) and anti-GluA3 (coral pink bar) antibodies and then preloaded with [^{3}H]D-Asp and exposed in superfusion to the complement (dilution 1:300) in presence of 10 µM DL-t-BOA (A) or in presence of 50 µM NBQX (B). DL-t-BOA and NBQX were added concomitantly to complement. Results are expressed as percentage of the tritium release evoked by complement from respective control synaptosomes (% of control). The complement-evoked release of [^{3}H]D-Asp amounted to 2,03 ± 0.23 (% of the total synaptosomal tritium content). Results are expressed as the mean ± SEM from 5 experiments run in triplicate. *$p < 0.05$ versus respective control; **$p < 0.01$ versus respective control.

1.2.2 Anti-GluA2 and anti-GluA3 antibodies mediate activation of the complement through the classical pathway

It was shown that complement releases glutamate from nerve terminals through a cascade of events involving the C1q-classical pathway (Merega et al., 2015). Synaptosomes were incubated with the anti-GluA antibodies and then exposed to the C1q-depleted complement (1:300) in the "up and down superfusion" system.

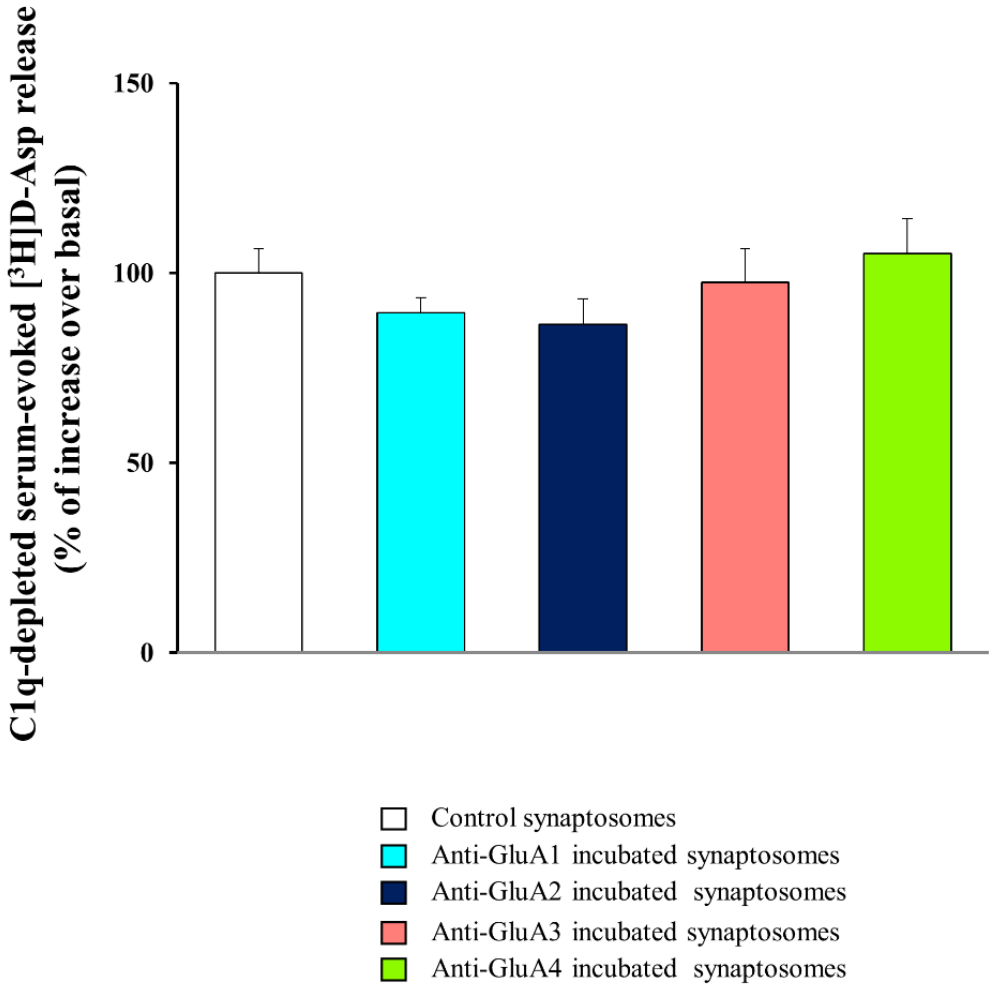


Figure 10: Effects of the incubation of mice cortical synaptosomes with anti-GluA subunit antibodies on the (1:300) C1q-depleted complement-evoked release of [^{3}H]D-Asp. Mice cortical synaptosomes were incubated in the absence (control) or in the presence of selected anti-GluA antibodies (as indicated) and then preloaded with tritium and exposed in superfusion to the C1q-depleted complement (dilution 1:300). Results are expressed as percentage of increase of the C1q-depleted complement evoked-[^{3}H]D-aspartate release (% of control) and are reported as the means ± S.E.M from three experiments run in triplicate.

The absence of the C1q component affected the complement-induced glutamate release from synaptosomes incubated with anti-GluA2 and anti-GluA3 when compared to control (Figure 10). The results confirmed that the releasing activity induced by the complement is conditioned by the presence of the C1q component, and thus by the activation of the classic pathway.

In conclusion, the results of this study describe two different events, both triggered by the presence of the anti-GluA2 and anti-GluA3 antibodies. The first is a *complement-independent* event causing the reinforcement of release of glutamate due to the increased insertion of the GluA2 and GluA3 subunit in the plasma membrane. The second is a *complement-dependent* event, which causes an overt release of glutamate because of the presence of the antigen-antibody complex.

Chapter 2.

AMPA autoreceptors and their relevance to autoimmune diseases: the case of frontotemporal dementia in humans

(Palese F, Bonomi E, Nuzzo T, Benussi A, Mellone M, Zianni E, Cisani F et al., 2020)

In the last years, a new player in the FTD pathogenesis came to the interest of the researchers: the autoimmunity. Particularly, the hypothesis relies on epidemiological and clinical studies showing an increased risk of autoimmune disorders and autoimmune system dysregulation in FTD patients (Sjögren and Wallin, 2001; Weintraub et al., 2006; Miller et al., 2013; Burberry et al., 2016; Cavazzana et al., 2018).

The hypothesis of an altered regulation of the immune system in frontotemporal dementia might open new routes for therapeutic perspectives acting at reducing or reverting the progression of autoimmune-related neurodegeneration.

Recently, Borroni and colleagues, identify both in the serum and in the CSF of FTD patients the presence of anti-GluA3 autoantibodies. The treatment of rat hippocampal neurons and human neurons derived from iPSCs with the CSF of patients positive for anti-GluA3 antibodies caused a detrimental effects (Borroni et al., 2017). Particularly, the treatment induces a reduction of the density of the AMPA receptors containing the GluA3 subunit at the post-synaptic level, but also it causes the reduction of the dendritic spine density (Borroni et al., 2017).

Based on evidence suggesting that the glutamatergic transmission in FTD patients is impaired, it became imperative to evaluate the impact of the sera (titled for anti-GluA3 antibodies) of FTD patients on glutamate release efficiency.

2.1 Effect of the CSF of patients suffering from frontotemporal dementia on the AMPA-evoked glutamate exocytosis from mice cortical synaptosomes.

To this aim I evaluated the effect of CSF from FTD patients having a different content of anti-GluA3 autoantibodies [positive for low (0,100 optical density, 450 nm) to high (0,341 optical density, 450 nm) anti-GluA3 antibody titer as well as CSF negative for anti-GluA3 antibody] on the glutamate release evoked by (S)AMPA from mice cortical synaptosomes (the CSF are made available to the study by Barbara Borroni). The cortical synaptosomes were incubated in presence of CSF positive or negative for anti-GluA3 antibody (1:100 and 1:200). Interestingly, the anti-GluA3-enriched antisera significantly reduced the AMPA-evoked glutamate release from mice cortical synaptosomes in a dilution-dependent manner (Figure 11A). Conversely, the absence of anti-GluA3 antibodies in the CSF of FTD patients didn't cause any changes in the (S)AMPA-evoked tritium release. The results were analyzed by correlating the release of glutamate from cortical incubated synaptosomes evoked by(S)AMPA exposed to the different dilutions (1:100 and 1:200), and the anti-GluA3 antibody titer of FTD patients. It emerged a strictly positive relationship between the two parameters (Palese et al., 2020; Figure 11B and C).

In conclusion, although the data were confirmatory of the fact that anti-GluA3 autoantibodies in the CSF could support functional impairment(s) at glutamatergic synapsis, they concomitantly suggested that the CSF outcome substantially differs from the effects elicited by the commercially available anti-GluA antibodies. Many events could underly the overt discrepancy, including the possibility that the CSF from FTD patients might contain other endogenous agents that could affect the anti-GluA

antibody/GluA subunit complex in synaptic plasma membranes i.e. then accelerating the internalization of the AMPA receptors instead of stabilizing it in synaptosomal membranes (see for the discussion Cisani et al., 2021). The data so far available does not allow to draw a definitive conclusion and further studies are needed to correctly address the point.

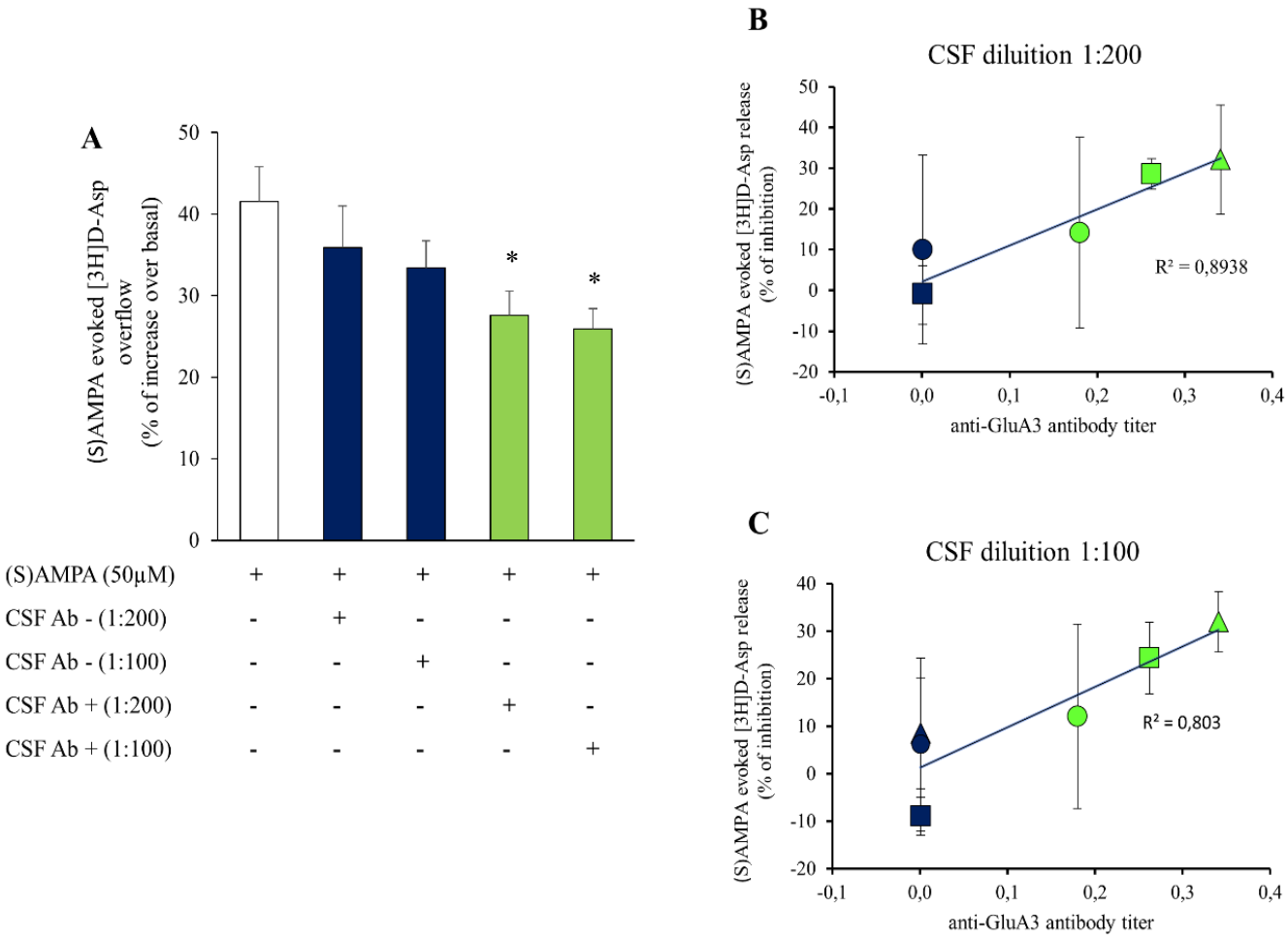


Figure 11. Effect of anti-GluA3 autoantibody on the AMPA-evoked glutamate release from mice cortical synaptosomes. (A). 50 µM (S)AMPA-evoked [^{3}H]D-Asp overflow from mice cortical synaptosomes incubated in the absence (white bar) or in the presence of CSFs (dilution as indicated) from patients without (CSF Ab -, blue bar, n=3) and with anti-GluA3 autoantibodies (CSF Ab +, green bar, n=3). Data are expressed as AMPA-evoked tritium overflow and are the means ± SEM of 3 experiments (run in triplicate) for each CSF. *p<0.05 versus control. (B and C). Correlation between the Ab -(blue symbols) and Ab +(green symbols) CSF-induced changes to the AMPA-evoked release of [^{3}H]D-Asp (expressed as % of inhibition) at 1:200 and 1:100 dilution (B and C respectively) and the respective anti-GluA3 autoantibodies titer for each CSF. The linear regression analysis coefficient (r2) is reported within the plot.

Chapter 3.

Early life programming of GluA2 and GluA3 subunits of AMPA receptors: long-term effects, sex differences and relevance for immune stress-related disorders

(Verhaeghe R, Gao V, Morley-Fletcher S, Bouwalerh H, Van Camp G, Cisani F et al., in positive revision)

As presented in the 3.2.2 section of the Introduction, early life stress occurring during the critical period of brain development profoundly shapes the health of an individual (Barker, 1995; Maccari et al., 2017). Adverse childhood experiences predict adult neurobiological, metabolic, and immune changes related to the development of age-related disease (Coe et al., 2007; Entringer et al., 2008, 2009; Li et al., 2010a). Several studies have in fact showed a link between early life stress experience and age-related conditions (Felitti et al., 1998; Thomas et al., 2008; Wegman and Stetler, 2009). This association has been also supported by the increasing evidence of accelerated aging induced by early life stress both in human and animals (Entringer et al., 2011, 2012; Danese and McEwen, 2012; Heidinger et al., 2012; Price et al., 2013; Haapanen et al., 2018; Marrocco et al., 2020).

Aging is a natural progressive physio-pathological process that determines a progressive loss of function leading to neurological symptoms and severe cognitive decline.

The old age is also characterized by a persistent elevated inflammatory state, which has a role in the functional decline and in many age-related diseases (Viviani and Boraso, 2011; Liu et al., 2017). Accordingly, augmented proinflammatory cytokines levels, including IFN-γ and IL-6, has been associated with type 2-diabetes, cardiovascular diseases, arthritis, certain cancer, osteoporosis, periodontal disease, and functional decline (Cannon, 1995; Ferrucci et al., 1999; Pradhan et al., 2001; Michaud et al., 2013; Franceschi and Campisi, 2014; Rea et al., 2018). Interestingly, young individuals that experienced early life stress display immune dysfunctions like that observed in elderly. In particular it has been shown that they have significantly higher circulating levels of IL-6, TNF-α and CRP with respect to control subject of the same age (Danese and McEwen, 2012; Baumeister et al., 2016).

Moreover, speaking of aging, it is worth mentioning the cellular aging and therefore the telomere shortening, which is one of the most relevant hallmarks of old age. Telomere shortening is a normal age-related process, however, it is accelerated in patients suffering from stress-related diseases such as mood disorders and major depression (Simon et al., 2006; Xie et al., 2017). Additionally, many studies have found a relationship between individuals that experienced childhood maltreatment or maternal deprivation and accelerated telomere shortening during life (Tyrka et al., 2010; Entringer et al., 2011; Kiecolt-Glaser et al., 2011; Drury et al., 2012; Asok et al., 2013). Thus, altogether these evidences support the hypothesis that stress exposure in the early phases of the development programs long-term trajectory that contributes to the accelerated aging in the adult individuals.

The rat model of perinatal stress, which combines prenatal stress and postnatal stress, can be used to study the impact and consequences of early life stress events on the organism and how they shape neurobehavioral adaptations to environmental challenges during the entire life span (Maccari et al., 2017, see section 3.2.2 of the Introduction). Clinical and preclinical studies found that early life stress experiences can cause persistent changes in the ability of the

HPA axis to respond to stress in adulthood (Glover and O'Connor, 2002; Seckl and Meaney, 2004). Accordingly, the PRS offspring are characterized by a dysregulation of the HPA axis (Maccari and Morley-Fletcher, 2007). In particular, the perinatal stress procedure causes an enhanced glucocorticoid release in pre-weaning rats and prolonged secretion of corticosterone after stress exposure in both adult and aged rats (Henry et al., 1994; Vallée et al., 1999). Additionally, PRS adult males present a decreased hippocampal neurogenesis (Lemaire et al., 2000), altered social memory and impaired synaptic plasticity (Brunson et al., 2005; Marrocco et al., 2012, 2014) in addition to increased level of proinflammatory cytokines (Vanbesien-Mailliot et al., 2007). Altogether these outcomes observed in adult male rats strongly support the hypothesis of early life stress-induced accelerated aging.

Such studies have been conducted in males rather than females. Only a limited amount of work has addressed the different response to early life stress with respect to biological sex. It has been shown that mGlu2/3 receptors are reduced in both sexes in adult PRS rats (Zuena et al., 2008), while the expression of mGluR5 was reduced only in the hippocampus of males PRS rats (Zuena et al., 2008). Sex-differences are also present in the hedonic sensitivity to highly palatable foods (Reynaert et al., 2016) and at a behavioral level (Zuena et al., 2008). Furthermore, gonadal hormones that contribute to sex differences in stress responsivity are modified by early life stress (Goel and Bale, 2008). For instance, plasma dihydrotestosterone levels are increased in adult males whereas adult female PRS rats display lower plasma estradiol levels (Reynaert et al., 2016). Interestingly, decreased sex hormone levels were also observed in middle-aged female rats (Van Camp et al., 2018), supporting again the hypothesis that early life stress accelerates aging. Moreover, these results highlighted that PRS induces alterations that are strictly sex dependent.

Remarkably, evidence showed that sex hormones could alter glutamatergic neurotransmission by regulating the expression of AMPA receptors (Diano et al., 1997;

D'Souza et al., 2003). The glutamatergic transmission in PRS rats is impaired as highlighted by the reduced expression of metabotropic glutamate receptors and the decreased glutamate release of adult male PRS rats from the ventral hippocampus (Zuena et al., 2008; Marrocco et al., 2012; Mairesse et al., 2015; Morley-Fletcher et al., 2018). However, the expression of AMPA receptors has not been yet investigated in this model. The literature regarding the changes induced by prenatal and postnatal stress in the expression of AMPARs subunits in the CNS remains conflictual (Bredy et al., 2004; Pickering et al., 2006; Yaka et al., 2007; Chocyk et al., 2013; Katsouli et al., 2014; Toya et al., 2014; Adrover et al., 2015), but it suggests that AMPA receptors play a role in the maladaptation induced by early life stress that need to be investigated. Therefore, I have evaluated the sex-dependent long-term effects induced by PRS on glutamatergic synapse focusing on the expression of AMPA receptors in the ventral hippocampus of adult rats of both sexes.

Although most of the studies described above shine light on effects of stress on adult age, little is known about the PRS effects on aged rats. Therefore, in order to give a clear and complete scenario about the long-term effects induced by early life stress, I have also analyzed the behaviors, the immune system, and expression of AMPA receptors in aged rats of both sexes in the prefrontal cortex, and ventral and dorsal hippocampus, since these are stress-related brain regions.

3.1 Sex and age-mediated IL-6, behavioral and synaptic modifications in PRS rats

(article in preparation)

The PRS protocol combines prenatal stress and postnatal stress (low maternal care) and represents a good model to study the long-term impact of early life stress. Adverse early life events, including disrupted maternal care, social deprivation, or abuse, if happened during a critical period for the developmental processes can profoundly affect the HPA axis functioning. Low maternal care induces in the offspring disrupted emotional behavior and hyperactivation of the HPA axis compared to offspring that received high maternal care (Francis et al., 1999; Caldji et al., 2000). Interestingly, the pathological phenotype observed in the early life stressed rats was reverted when they were adopted by unstressed mothers (Maccari et al., 1995). The adoption, in fact, increased the maternal behavior and reduced the secretion peak of corticosterone observed in the adult PRS offspring (Maccari et al., 1995). For these reasons, is important to analyze the active maternal behavior of stressed and unstressed mothers, measured as a % of the frequency of nursing behavior, grooming, licking, and carrying pups (Champagne et al., 2003).

Figure 12 showed a significant reduction of the active maternal behavior of stressed mothers compared to unstressed on the second and third day after the birth of the offspring. To note, only the offspring that received significant low maternal care on day 3 have been used as PRS animals.

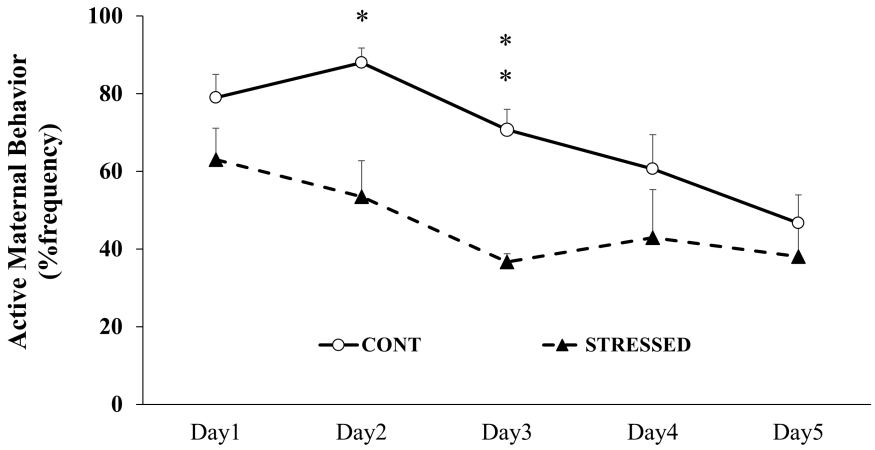


Figure 12. Analysis of the maternal behavior. Maternal active behavior measured in the first five days postpartum in control and stressed mothers. Values are means ± SEM of 5 females per group. * $p < 0.05$ Stressed dams versus control; ** $p < 0.01$ Stressed dams versus control.

Several clinical observations suggested an association between early life stress, disturbances of the HPA axis and increased vulnerability to developing altered emotional behavior such as anxiety and depression (Shea et al., 2005; Lopez-Duran et al., 2009; Guerry and Hastings, 2011; Du and Pang, 2015). For this reason, I have analyzed the impact of early life stress on the emotional behavior, measured as risk-taking behavior, in adult and aged rats of both sexes. The risk-taking behavior was assessed in the elevated plus maze (EPM) analyzing both the time spent in the open arm and the latency to the open arm. The results showed that adult male PRS rats spent less time in the open arm and displayed an increased latency to open arm than male control. These results reflected a decrease in risk-taking behavior of adult male PRS rats (Figure 13A and B, but see also Zuena et al., 2008; Marrocco et al., 2012, 2014; Morley-Fletcher et al., 2018). Interestingly, aged male PRS rats presented the same behavioral profile as adult males (Figure 13C and D). In adult and aged female rats, conversely, PRS decreased the latency to the open arm and increased the time spent in the open arm, although in adult female PRS not significantly. I also found a clear-cut sex effect for unstressed

control rats, with increased latency to the open arm in females compared to males of both ages. Thereby, these results highlighted that PRS programs behavioral alterations that are sex dependent. Additionally, these data suggested that the sex-dependent alterations caused by early life stress are persistent and uniform across life span.

It is nowadays well established that inflammation highly contributes to behavioral changes associated with age and age-related disorders (Simen et al., 2011; Perna et al., 2016; Squassina et al., 2019). For example patients with major depression and personality disorders presented a significant rise in serum levels of proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12, and IFN-γ (Maes et al., 1999; Hestad et al., 2003; Raison et al., 2006). Accordingly, IL-6 know-out animals exhibit resistance to stress-induced depressive- and anxiety-like behaviors (Chourbaji et al., 2006). The inflammatory state has been found increased also in patients that experienced adverse events early in life. Particularly, they showed elevated circulating levels of IL-6, TNF-α, and CRP compare to control (Danese and McEwen, 2012; Baumeister et al., 2016). Another interesting study unveiled that the expression of proinflammatory genes, including TNF-α , IL-1, and IL-6, was increased in the monocytes of the offspring of patients with personal disorders (Padmos et al., 2008). These data suggest a link between early life stress, inflammatory state, and age-related psychiatric disorders. In this context it has been proposed that the quantification of the peripheral bioavailability of circulating cytokines could be a predictive marker of the central and behavioral alterations of age-related diseases. In this perspective, I focused on the proinflammatory cytokines IL-6 (Zhang et al., 2017), since the old age is characterized by an enhanced activity of the immune system, which translates into an elevated production of IL-6 (Ye and Johnson, 1999, 2001), a proinflammatory cytokines that has been also associated with shorter telomere length (Fitzpatrick et al., 2007; Carrero et al., 2008).

The analysis of the plasmatic concentration of the IL-6 showed that PRS increased the levels of this proinflammatory cytokine in aged males (Figure 13E). This result is in accordance with the previous studies showing that adult males PRS rats presented an increased level of proinflammatory cytokines, such as IFN-γ (Vanbesien-Mailliot et al., 2007), supporting the hypothesis that early life exposure to stress events causes anticipated aging.

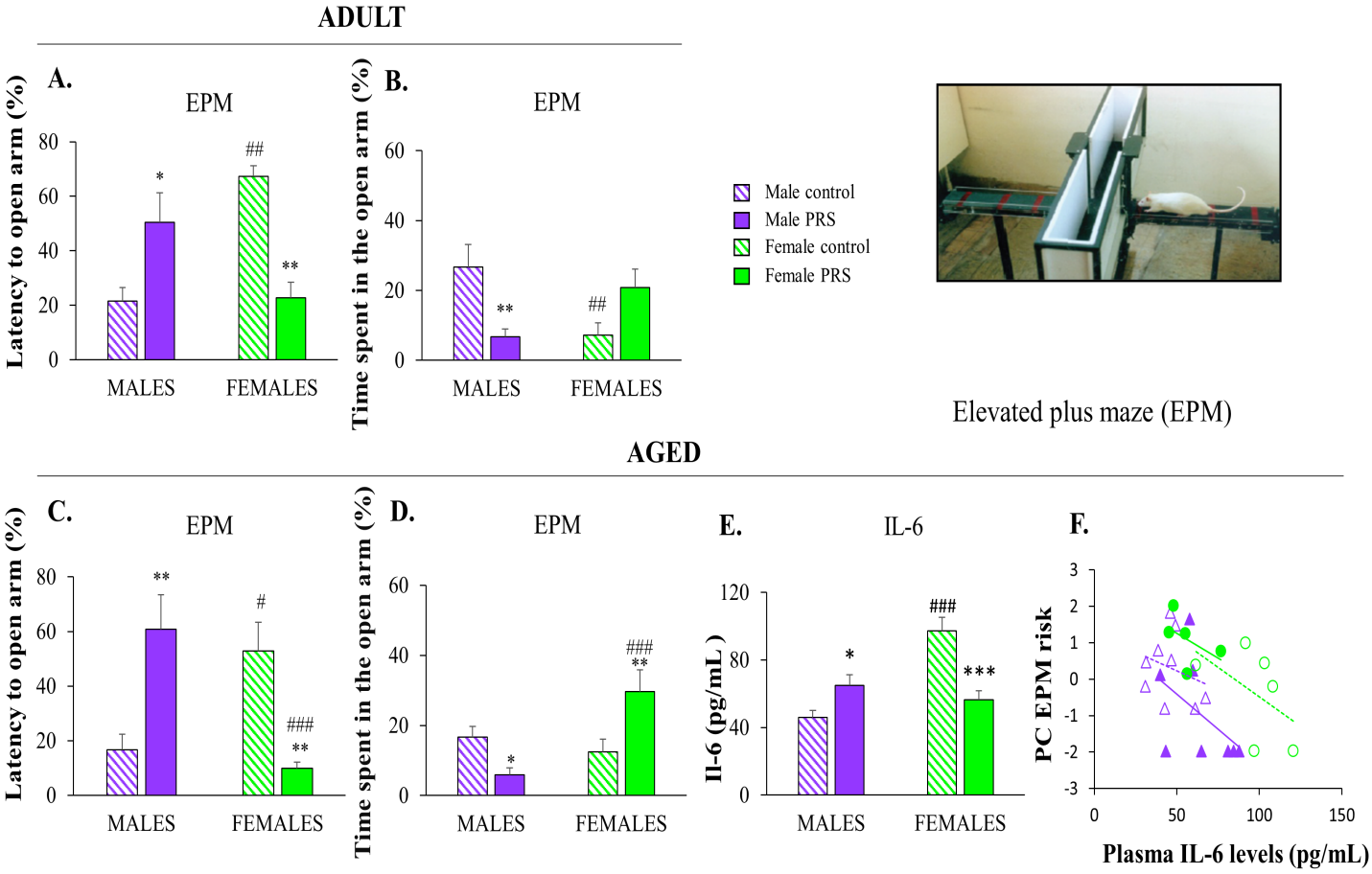


Figure 13. The effect of sex and PRS on the risk-taking behavior in adult and aged rats and on IL-6 in aged rats. A, B, C and D. Risk-taking behavior has been assessed in the elevated plus maze (n=6-8 rats per group) in adult (2A and B) and aged (2C and D) control and PRS rats of both sexes. The latency to open arm and the time spent in open arm were the two parameters analyzed. Values are expressed as means ± S.E.M., Control vs PRS * = p<0.05; **= p<0.01. Males vs Females # = p<0.05; ##= p<0.01; ###= p<0.001. E. The interleukin-6 (pg/m) level was measured in plasma extracted from blood samples of aged male and female control and PRS rats (n= 8 rats per group) and measured with ELISA kit. The partial correlation between the risk-taking behavior and IL-6 is represented in 2F. Control vs PRS * = p<0.05; ***= p<0.01. Males vs Females ###= p<0.001.

Interestingly, PRS in females decreased plasmatic levels of IL-6 with respect to control. Since IL-6 levels increase with age in both rats (Foster et al., 1992) and humans (Fagiolo et al., 1993), these findings suggest that females are protected against age-dependent inflammation caused by early life stress. Moreover, I have performed a partial correlation to determine the relationship between the risk-taking behavior and the proinflammatory cytokine and I found that the aged male PRS rats, which present higher levels of IL-6 showed a reduced risk-taking behavior in the EPM (Figure 13F) suggesting a direct relationship between the two parameters.

Along with inflammation, many neurological disorders has been linked to impairment of the dopaminergic (Baier et al., 2012), as well as serotoninergic and noradrenergic system (Suzuki et al., 2010). In the last year, new evidence established that anxiety and depressive-like behavior are also associated with alterations in the balance between excitatory and inhibitory transmission (Tordera et al., 2007; Garcia-Garcia et al., 2009; Chen et al., 2010; Popoli et al., 2012). Hippocampal glutamatergic transmission is significantly affected in depressed patients as well as in animals exposed to stress (Sanacora et al., 2012). For instance, PRS induced a dramatical reduction of glutamate release evoked by a depolarizing stimulus from the ventral hippocampus, a region involved in emotion and anxiety, but not from the dorsal hippocampus of adult male rats (Marrocco et al., 2012; Mairesse et al., 2015; Morley-Fletcher et al., 2018).

Interestingly, the spontaneous release of glutamate from PRS rats was not affected, suggesting that the alteration in the exocytosis of glutamate may involve the presynaptic exocytotic machinery, which mediates the fusion of synaptic vesicles within the presynaptic membrane. Accordingly, the expression of the synaptic vesicle-associated proteins, including Rab3a, Munc-18, Synapsin IIa, vesicle-associated membrane proteins (VAMP), Syntaxin and Synaptophysin (SYP), was found to be significantly reduced in the ventral hippocampal synaptosomes of adult male PRS rats (Figure 14, but see also Marrocco et al., 2012, 2014;

Morley-Fletcher et al., 2018). Conversely, no changes were observed in adult female PRS rats with respect to controls (Figure 14). Notably, I observed a similar scenario, with a selective sexually dimorphic effect also in the ventral hippocampus of aged rats. PRS reduced the expression of Rab3a and Syntaxin in aged male rats, while no alterations were found in the expression of synaptic-vesicles proteins in female PRS rats (Figure 14). Moreover, I found a clear-cut sex effect for the expression of synaptic vesicle-associated proteins in both adult unstressed rats, with a reduced expression level of Munc-18, VAMP, Synapsin IIa and Syntaxin in females compared to males, and aged rats with females expressing lower levels of Syntaxin and Rab3a than males.

Altogether these results showed that males and females are differentially affected by PRS-induced changes, and that these changes are persistent during the life span.

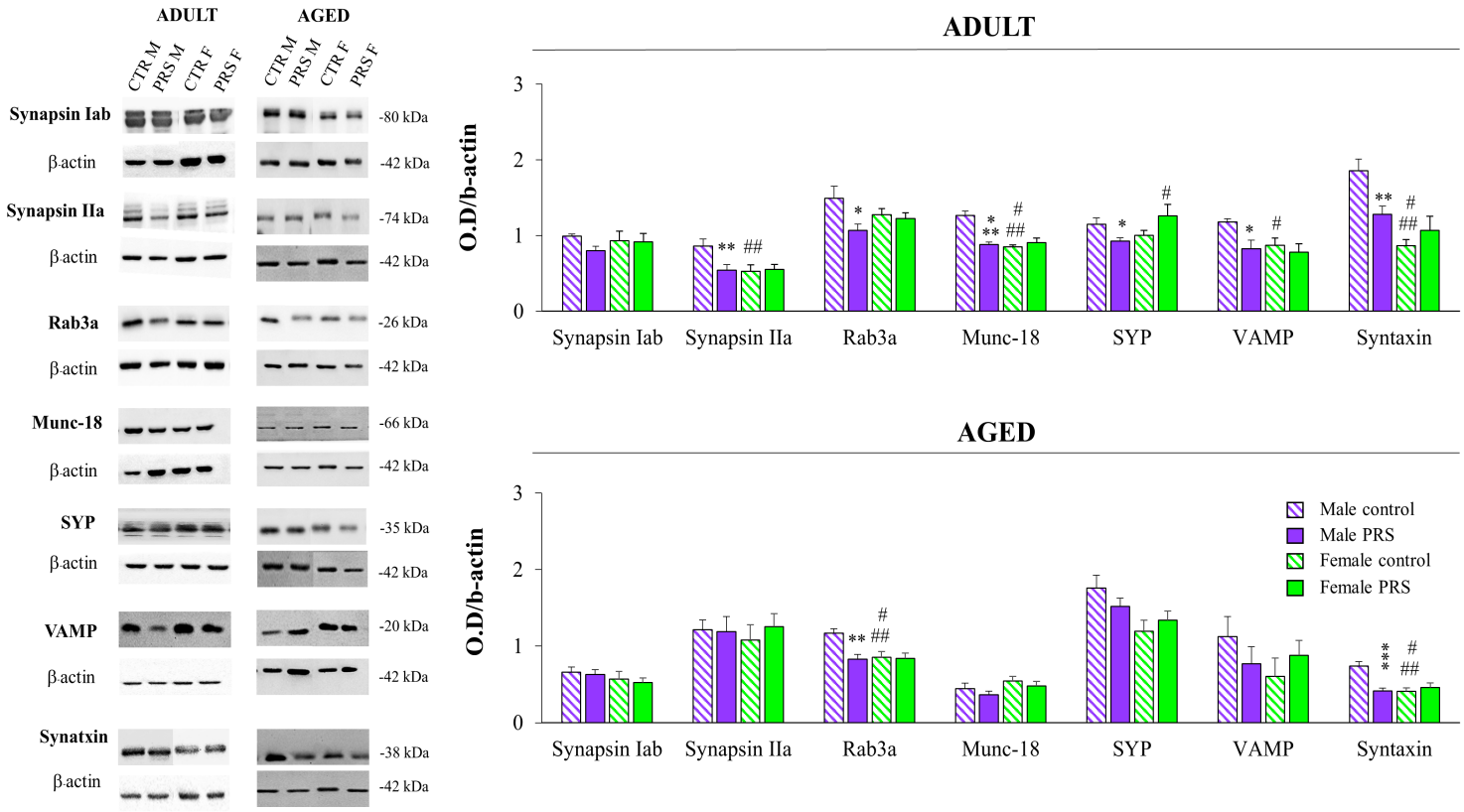


Figure 14. Effect of sex and PRS on the expression of synaptic vesicle-associated proteins in the ventral hippocampus of adult and aged rats. Immunoblot analysis of synaptic vesicle-associated proteins in synaptosomal fractions obtained from the ventral hippocampus of adult male and female PRS and control rats (upper panel) and aged male and female PRS and control rats (lower panel). The left panel shows representative blots (n=6-8 rats per group). Values are expressed as means ± S.E.M., Control vs PRS * = $p<0.05$; **= $p<0.01$; ***= $p<0.01$. Males vs Females # = $p<0.05$; ##= $p<0.01$; ###= $p<0.001$.

3.2 Sex and age-related modifications of spatial recognition memory and AMPA receptors density in selected brain regions of PRS rats

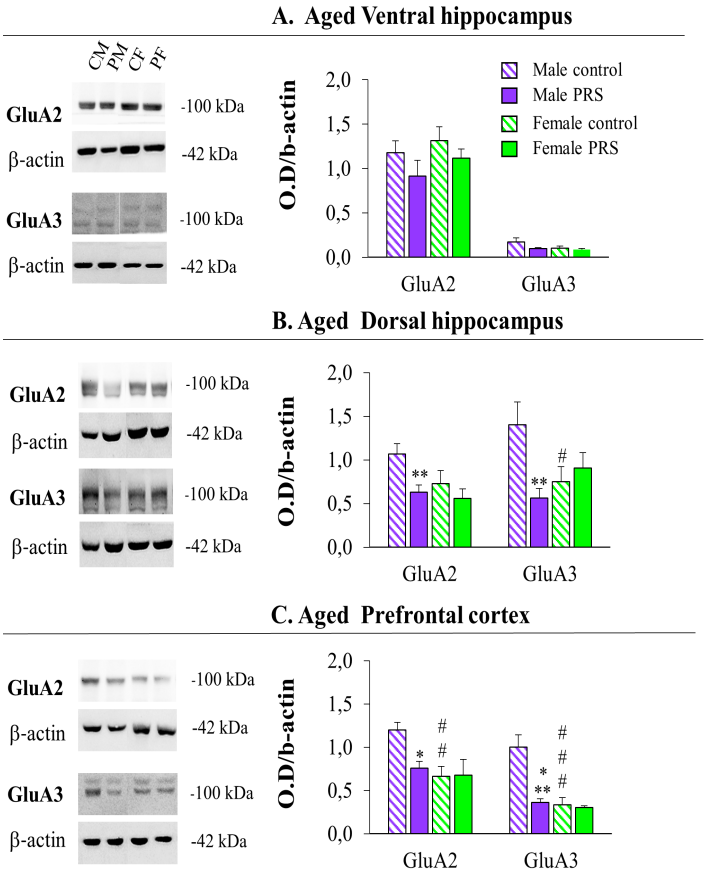
In the recent years, several findings suggested that the altered bioavailability of cellular immune modulators such as cytokines could modulate the efficiency of the glutamatergic-dependent synaptic transmission (Pickering et al., 2005; Centonze et al., 2009; Di Filippo et al., 2013; Stampanoni Bassi et al., 2019; Bruno et al., 2020). Interestingly, IL1β has been reported to directly influence the molecular composition of the glutamatergic synapse and NMDA receptor signaling (Viviani et al., 2003, 2006). While IL1β preferentially affects NMDA receptors, TNF- α directly interacts with AMPA receptors through TNF-R1 (Vezzani and Viviani, 2015). A recent work demonstrated also a link between IL-6 and AMPA receptors-mediated signaling at the post-synaptic level (Hettinger et al., 2018). Accordingly, the treatment with NBQX ameliorate the inflammation state of the antigen-induced arthritis rats by reducing the expression of IL-6 in the serum (Bonnet et al., 2015). Based on such evidence and taking in account the previously showed alteration of the level of proinflammatory cytokines such as IL-6 and IFN-γ (Vanbesien-Mailliot et al., 2007) induced by PRS, I expected to observe some variations in the expression and/or insertion in the membrane of the corresponding ionotropic glutamate receptors, which are those that represent the sensors of the efficiency of the glutamate release. In this case, AMPA receptors, which have an expression and insertion in membrane correlated to the efficiency of the glutamate signal, represent an excellent indicator of the functioning of the excitatory synapse. While GluA1 is necessary for the delivery of AMPA receptors during LTP (regulated trafficking), GluA2/GluA3-containing AMPA receptors replace the preexisting AMPA receptors containing the GluA1 subunits in an activity-independent manner (constitutive trafficking, Henley et al., 2011). Recent evidence showed that the GluA3 subunit is involved in memory processes (Reinders et al., 2016) may

suggesting that the constitutive trafficking represents a molecular mechanism for memory consolidation. For this reason, since aging determine a progressive loss of function and defects in cognitive capabilities such as spatial and working memory, I have firstly evaluated whether PRS causes alterations in the spatial recognition memory of aged rats of both sexes.

The analysis was performed with the Y-maze and the spatial recognition memory was measured as a recognition score. The recognition score was changed driven by the reduced time spent in the novel arm in PRS males with respect to control rats. No changes were observed between control and PRS females (Figure 15E). Thereby, early life stress reduced spatial memory acquisition only in aged males. These results are also consistent with previous findings obtained in males (Vallee et al., 1999). The cognitive decline, which is an unavoidable consequence of aging, is mediated through alterations of the number and function of synaptic receptors, mainly AMPA receptors, in brain regions responsible for memory-related tasks (Shi et al., 2007; Henley and Wilkinson, 2013). The composition of AMPA receptor subunits undergoes dynamic changes following exposure to a variety of stimulus such as sensory experience, emotional stress, cocaine use, learning, and social isolation (Goel et al., 2006; Plant et al., 2006; Conrad et al., 2008; Clem and Huganir, 2010; Liu et al., 2010; Schmidt et al., 2010; Mameli et al., 2011). Therefore, based on such evidence and on the previous ones showing that proinflammatory cytokines modulate the efficiency of the glutamatergic transmission (Bonnet et al., 2015; Vezzani and Viviani, 2015; Hettinger et al., 2018), I evaluated the long-lasting alterations induced by early life stress on the expression of the GluA2 and GluA3 subunits of AMPA receptors, firstly in the ventral hippocampus and then in other different brain regions responsible for memory-related tasks, such as the dorsal hippocampus and prefrontal cortex.

I found no differences in the expression of the GluA2 and GluA3 subunits in the ventral hippocampus of either adult or aged PRS rats of both sexes (Figure 15A and D), suggesting that GluA2 and GluA3 subunits are not directly implicated on the altered glutamate exocytosis

from the ventral hippocampus. However, I observed a clear reduction of the density of both GluA2 and GluA3 subunits in the dorsal hippocampus and prefrontal cortex of aged male PRS rats with respect to control, whereas no differences have been found in females (Figure 15 B and C).



D. Adult Ventral hippocampus

O.D/b-actin	Male CTR	Male PRS	Female CTR	Female PRS
GluA2	1,14 ± 0,18	1,33 ± 0,17	1,02 ± 0,06	1,18 ± 0,03
GluA3	0,77 ± 0,10	1,14 ± 0,18	0,72 ± 0,13	0,78 ± 0,17

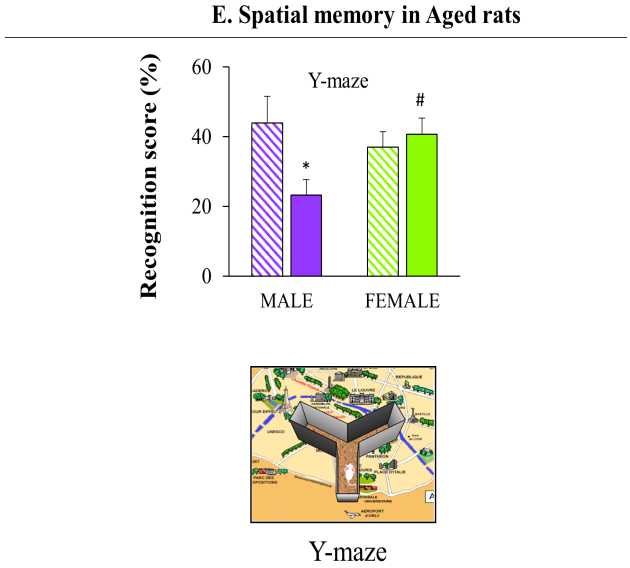


Figure 15. Effect of sex and PRS on the expression of GluA2 and GluA3 subunits in stress-related region of adult and aged rats and on the spatial memory in aged rats. A, B and C. Representative blots (n=6-8 rats per group) and Immunoblot analysis of GluA2 and GluA3 subunits of AMPA receptor in synaptosomal fractions obtained from the ventral hippocampus (4A), dorsal hippocampus (4B) and prefrontal cortex (4C) of aged male and female PRS (PM and PF respectively) and control rats (CM and CF, respectively). Values are expressed as means ± S.E.M., Control vs PRS * = $p<0.05$; **= $p<0.01$; ***= $p<0.01$. Males vs Females # = $p<0.05$; ##= $p<0.01$; ###= $p<0.001$. D. Immunoblot analysis of GluA2 and GluA3 subunits of AMPA receptor in synaptosomal fractions obtained from the ventral hippocampus of adult rats (n=6-8 rats per group) did not differ from PRS and control rats. A sex dimorphic effect has been found within PRS in the expression of GluA3 subunits. Values are expressed as means ± S.E.M., Males vs Females # = $p<0.05$. E. The spatial recognition memory was study using the Y-maze (n=8 rats per group) in aged male and female control and PRS. The % of the recognition score was the parameter analyzed. Values are expressed as means ± S.E.M., Control vs PRS * = $p<0.05$. Males vs Females # = $p<0.05$.

The absence of PRS-induced effect on the AMPA subunits expression in females, combined with the previous data, suggested that they are resilient to changes in neuroplasticity induced by PRS. In addition, these results unveiled a sex difference in the expression of GluA2 in the prefrontal cortex and of GluA3 both in prefrontal cortex and dorsal hippocampus of control animals. In order to explain the reduced synaptic expression of AMPA receptor subunits in the dorsal hippocampus and prefrontal cortex of aged male rats is necessary reminding that the prefrontal cortex is implicated in the working memory and the dorsal hippocampus in cognitive functions, such as learning and memory and spatial memory acquisition (Fanselow and Dong, 2010). Thus, the selective decrease of the synaptic expression of GluA2 and GluA3 subunits found in these two brain regions, could correlate with the reduced spatial memory observed in aged PRS rats performing the Y-maze. Females PRS rats did not present changes neither in the expression of GluA2 and GluA3 subunits or in the spatial recognition memory, supporting the direct relationship between the two parameters.

Interestingly, Morley-Fletcher end co-workers in 2018 found that treatment of adult male PRS rats with the AMPA PAM S 47445 was able to revert the pathological phenotype observed in the offspring. In particular, the treatment normalized the low social memory performance of PRS rats (Morley-Fletcher et al., 2018), suggesting a role for AMPA receptors in the cognitive and memory decline induced by early life stress. Moreover, data in literature have demonstrated that male offspring of high-licking and grooming-arched back nursing mothers showed increased GluA1 and GluA3 mRNA levels in the hippocampus (Bredy et al., 2004). Similarly results showing raised levels of GluA1 and GluA2 subunits in the prefrontal cortex have been observed in adolescent offspring submitted to maternal separation, which is known to increase maternal care (Chocyk et al., 2013). On the other hand, maternal deprivation or prenatal stress, which have the opposite effects with respect to maternal separation, results in decreased levels of AMPA receptors (Pickering et al., 2006; Yaka et al., 2007; Toya et al.,

2014). Overall, this indicates that maternal behavior itself affects the development of the glutamatergic system, since maternal care increases the expression of ionotropic glutamate receptors (Bredy et al., 2004; Chocyk et al., 2013) while disrupted maternal care, as in the PRS rat model, decreased their expression (Pickering et al., 2006; Yaka et al., 2007; Toya et al., 2014).

In conclusion, all the findings reinforce the idea that early life stress causes long-lasting effects on brain development and provide the first evidence that long-term programming effects induced by PRS are strictly sex-dependent.

GENERAL DISCUSSION AND CONCLUSION

The main objective of my PhD program was to explore the roles of AMPA receptors in the CNS. The project was developed in two different laboratories, at the Department of Pharmacy, University of Genoa and at the Glyco-stress laboratory, University of Lille, by using different animal models to investigate the expression, the pharmacological profile and the physio-pathological roles of these receptors on glutamatergic transmission.

The main field of research of the laboratory headed by Anna Pittaluga is the pharmacological and functional characterization of presynaptic release-regulating receptors in nerve endings. By taking advantage of pharmacological approach set up in this laboratory (i.e. the immune pharmacological approach) I tried to answer the so far unsolved question of the subunit composition of the cortical AMPA autoreceptors and concomitantly to investigate whether and how antibodies can impact their presynaptic release-regulating activity, in an attempt to implement the knowledge of the central molecular events involved in autoimmune diseases typified by the overproduction of anti-GluA antibodies.

Differently, the laboratory headed by Sara Morley-Fletcher at the University of Lille is internationally recognized for the study of the impact of the prenatal stress on the central glutamate transmission. In this lab I had the opportunity to investigate the fate and the expression of the AMPA subunits in selected regions of the CNS in both PRS male and female rats at different ages. I correlated the behavioral and neurobiochemical alterations to deepen the knowledge of these receptors in the early life stress-related disorders.

The following results represent the main findings of my work:

1. Cortical AMPA autoreceptors in mice preferentially consist of GluA2/GluA3 subunits, which trafficking in a constitutive way

I confirmed the presence of presynaptic release-regulating AMPA autoreceptors in cortical synaptosomes, also demonstrating that they traffic in a constitutive manner in plasma membranes. Then, by applying the "immuno-pharmacological approach" I demonstrated that the anti-GluA2 and anti-GluA3 antibodies modified the releasing activity of the presynaptic AMPA autoreceptors as well as their insertion in the synaptosomal plasma membrane.

2. Antibodies anti-GluA2 and anti-GluA3 are responsible for a *complement-independent* and a *complement-dependent* increase of glutamate exocytosis

The presence of the antigen-antibody complex at the outer side of synaptosomal particles also triggers the activation of the complement through the classic pathway. In particular I highlighted the multifaceted impact of the anti-GluA3 antibodies at chemical synapsis, which consists of both *complement-independent* and *complement-dependent* events that affect glutamate release and that maybe relevant to comprehend the pathological events.

3. The sera from patients suffering from frontotemporal dementia containing anti-GluA3 antibodies reduces the releasing activity elicited by AMPA autoreceptors

An important result of my work was that the data obtained with commercially available antibodies cannot recapitulate the detrimental effects occurring in the CNS of patients suffering from an autoimmune disease typified by the overproduction of anti-GluA3 autoantibodies (i.e. the FTD). In fact, the anti-GluA3-enriched CSFs of FTD patients inhibited instead of potentiating the AMPA autoreceptors controlling glutamate exocytosis, as indeed observed with the commercial anti-GluA3 antibodies. Further studies are needed to correctly address the point.

4. Alterations of the glutamatergic synapse lies at the core of PRS phenotype across the lifespan: focus on AMPA receptors.

I found that aged male PRS rats displayed a significant decrease of GluA2 and GluA3 both in the dorsal hippocampus and prefrontal cortex, which are brain regions that are mainly involved in stress responses and in memory processes. Differently, the expression of AMPA receptor subunits GluA2 and GluA3 was not altered in the ventral hippocampus of both adult and aged rats of both sexes. The reduced expression of GluA2 and GluA3 in the dorsal hippocampus and prefrontal cortex appears to be causally related to the decreased spatial memory recognition observed in aged males.

5. The long-term programming triggered by PRS is strictly sex dependent.

I observed a sex dependent effect induced by PRS in the expression of the vesicle-associated proteins, which are reduced both in adult and aged male PRS but not in females suggesting that females are protected against early life stress. I also observed a sex-dimorphic effect induced by PRS analyzing the density of the GluA2 and GluA3 subunit in the dorsal hippocampus and prefrontal cortex, which was reduced in aged PRS males but not in females. This result in turn reflects the reduced spatial memory recognition observed exclusively in PRS males. Interestingly, early life stress in females enhanced the risk-taking behavior and decreased the plasmatic levels IL-6 levels supporting the hypothesis that females are protected against PRS-induced detrimental effects.

In conclusion, I have confirmed the plasticity of the GluA2 subunit and its key role in pathophysiological conditions, but, even more relevant, I provide clear evidence of the main role of the GluA3 subunit in controlling glutamate exocytosis in autoimmune diseases and stress-related disorders.

As to the GluA2 subunits, I confirmed that they traffic presynaptically in a constitutive way also in the cortex and that this in-out movements are selectively targeted by antibodies recognizing the amino-terminus of the GluA2 and the GluA3 subunits, unveiling new unexpected molecular events that could support the detrimental effects of autoantibodies in this CNS region. I also highlighted significant changes in the expression of the GluA2 subunit in aged stressed rats that could be causally related to the deficit of spatial learning memory observed in these animals and in general to their pathological phenotype.

The novelty of this study, however, concerns the results about the GluA3 subunit, which highlighted their relevance in the control of glutamate transmission in different brain areas. The results clearly indicate the GluA3 subunit as a key player in the immunological adaptations that take place in stress-related disorders and autoimmune diseases, posing however questions on the real impact of the anti-GluA3 antibodies in the CNS of patients suffering from FTD.

Last but not the least, I provided evidence suggesting a sex difference in the expression of GluA2 and GluA3 subunits in rats. Particularly, I showed a higher expression of GluA2 and GluA3 subunits in the prefrontal cortex of aged male control animals with respect to females and an increased expression of the GluA3 subunit in the dorsal hippocampus of aged males compared to females.

In a whole, these results suggest that knowing more about AMPA receptors subunits will yield much insight in understanding brain functions.

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